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(54) Title: 8-AZA-BICYCLO[3.2.1]OCTANE NMDA/NR2B ANTAGONISTS

(57) Abstract: Novel 3-substituted 8-aza-bicyclo[3.2.1]octanes (commonly known as "tropamines") substituted in the 8-position are effective as NMDA NR2B antagonists useful for relieving pain.

## TITLE OF THE INVENTION

5           8-AZA-BICYCLO[3.2.1]OCTANE NMDA/NR2B ANTAGONISTS

## BACKGROUND OF THE INVENTION

## Field of the Invention

10          This invention relates to novel 8-aza-bicyclo[3.2.1]octanes. In particular, this invention relates to novel 3-substituted 8-aza-bicyclo[3.2.1]octanes substituted in the 8-position that are effective as NMDA NR2B antagonists useful for relieving pain.

15          Ions such as glutamate play a key role in processes related to chronic pain and pain-associated neurotoxicity – primarily by acting through N-methyl-D-aspartate (“NMDA”) receptors. Thus, inhibition of such action – by employing ion channel antagonists, particularly NMDA antagonists – can be beneficial in the treatment and control of pain.

20          Known NMDA antagonists include ketamine, dextromophan, and 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (“CPP”). Although these compounds have been reported to produce symptomatic relief in a number of neuropathies including postherpetic neuralgia, central pain from spinal cord injury, and phantom limb pain, (J.D. Kristensen, et al., *Pain*, 51:249-253 (1992); K. Eide, et al., *Pain*, 61:221-228 (1995); D.J. Knox, et al., *Anaesth. Intensive Care* 23:620-622 (1995); and M.B. Max, et al., *Clin. Neuropharmacol.* 18:360-368 (1995)) widespread use of these compounds is precluded by their undesirable side effects. Such side effects at analgesic doses include psychotomimetic effects such as dizziness, headache, hallucinations, dysphoria, and disturbances of cognitive and motor function. Additionally, more severe hallucinations, sedation, and ataxia are produced at doses only marginally higher than analgesic doses. Thus, it would be desirable to provide novel NMDA antagonists that are absent of undesirable side effects or that produces fewer and/or milder side effects.

25          NMDA receptors are heteromeric assemblies of subunits, of which two major subunit families designated NR1 and NR2 have been cloned. Without being bound by theory, it is generally believed that the various functional NMDA receptors

in the mammalian central nervous system ("CNS") are only formed by combinations of NR1 and NR2 subunits, which respectively express glycine and glutamate recognition sites. The NR2 subunit family is in turn divided into four individual subunit types: NR2A, NR2B, NR2C, and NR2D. I. Ishii, et al., *J. Biol. Chem.*, 268:2836-2843 (1993), A. Wenel, et al., *NeuralReport*, 7:45-48 (1995), and D.J. Laurie et al., *Mol. Brain Res.*, 51:23-32 (1997) describe how the various resulting combinations produce a variety of NMDA receptors differing in physiological and pharmacological properties such as ion gating properties, magnesium sensitivity, pharmacological profile, as well as in anatomical distribution.

For example, while NR1 is found throughout the brain, NR2 subunits are differentially distributed. In particular, it is believed that the distribution map for NR2B lowers the probability of side effects while producing pain relief. For example, S. Boyce, et al., *Neuropharmacology*, 38:611-623(1999) describes the effect of selective NMDA NR2B antagonists on pain with reduced side-effects. Thus, it would be desirable to provide novel NMDA antagonists that target the NR2B receptor.

International Patent Publication WO94/21615 describes benzimidazole-piperidine compounds utilized as dopamine D4 antagonists. Phenol compounds described as NMDA antagonists are described in U.S. patent Nos. 5,306,723 and 5,436,255, and in International Patent Publications WO91/17156, WO92/19502, WO93/02052, WO94/29571, WO95/28057, WO96/37226, and EP 04422506. Benzyl piperidines substituted with phenols or imidazoles are described in Z.-L. Zhou, et al., *J. Medicinal Chemistry*, 42:2993-3000(1999); T.F. Gregory, et al., Poster #94, 218<sup>th</sup> National Meeting American Chemical Society, New Orleans, Louisiana, August 22-26, 1999. Other NMDA NR2B selective compounds are described in European Patent Publication EP 787493 and *British J. Pharmacol.*, 123:463(1998). However, there continues to be a need for novel NMDA antagonists that target the NR2B receptor.

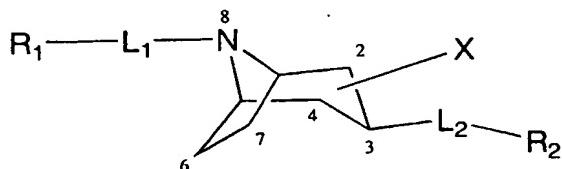
## SUMMARY OF THE INVENTION

The present invention relates to 3-substituted 8-aza-bicyclo[3.2.1]octanes substituted in the 8-position with benzimidazoles, imidazopyridines, phenols or imidazoles either directly or through a C1-C4alkyl, cycloalkyl, hydroxyalkyl, alkoxy or aminoalkyl chain. The present invention also forms novel pharmaceutical compositions utilizing these novel compounds. Further, this invention includes novel methods to treat pain by utilizing the novel compounds.

## DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the compounds of this invention are 3-substituted 8-aza-bicyclo[3.2.1]octanes (commonly known as "tropanes") represented by Formula (I):

5



(I)

or pharmaceutically acceptable salts thereof, wherein

R<sub>1</sub> is benzimidazole, imidazole, imidazopyridine, indole, quinazoline, purine, benzoxazolone, or phenol;

10 R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl, hydroxy, or carboxy;

15 L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, aminoC<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-C<sub>6</sub>alkyl, or aminocarbonyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

20 In one embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is benzimidazole;

R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl, hydroxy, or carboxy;

25 L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, aminoC<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-C<sub>6</sub>alkyl or aminocarbonyl; and

30 optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

In another embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is imidazole;

R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each 5 substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl, hydroxy, or carboxy;

L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, aminoC<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-C<sub>6</sub>alkyl or aminocarbonyl; and

10 optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

In yet another embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

15 R<sub>1</sub> is imidazopyridine;

R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl, hydroxy, or carboxy;

L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, aminoC<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-C<sub>6</sub>alkyl or aminocarbonyl; and

20 optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

25 In still another embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is purine;

30 R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl, hydroxy, or carboxy;

L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, amino, C<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-C<sub>6</sub>alkyl or aminocarbonyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

In another embodiment, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub> is phenol;

R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl, hydroxy, or carboxy;

L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, aminoC<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-C<sub>6</sub>alkyl or aminocarbonyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-decahydronaphthalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

Unless otherwise stated, the terms "carbonyl" and "aminocarbonyl" include short C<sub>1</sub>-C<sub>2</sub> termini. The terms include, for example, -CH<sub>2</sub>CONH-, -CH<sub>2</sub>CO-, -C<sub>2</sub>H<sub>4</sub>CONHCH<sub>2</sub>-, and -CH<sub>2</sub>COC<sub>2</sub>H<sub>4</sub>-.

Unless otherwise stated, the term "carbamate" is used to include -OCOOC<sub>1</sub>-C<sub>4</sub>alkyl, -NHCOOC<sub>1</sub>-C<sub>4</sub>alkyl, and -OCONHC<sub>1</sub>-C<sub>4</sub>alkyl.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

- 5        The term "SEM" is used to describe -CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-Si(CH<sub>3</sub>)<sub>3</sub>.  
The term "C<sub>0</sub>" means that the carbon is not present. Thus, "C<sub>0</sub>-C<sub>5</sub>" means that there are from none to five carbons present – that is, five, four, three, two, one, or no carbons present.

10      The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

15      Compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included.  
20      During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

25      The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed 30 include ion exchange resins such as, for example, arginine, betaine, caffeine, choline,  
35

N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, 5 procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for 10 example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

15 The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and 20 intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

25 In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., 30 oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid,

as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of 5 the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired 10 presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one 15 or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers 20 include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as 25 starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous 30 techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, 35 optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing

agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 1mg to about 500mg of the active ingredient and each 5 cachet or capsule preferably containing from about 1 to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid 10 polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous 15 preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion 20 medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for 25 use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a 30 desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently

formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or 5 more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may 10 also be prepared in powder or liquid concentrate form.

### EXPERIMENTAL PROTOCOLS

#### **Assessing the Activity of Selected Compounds to Inhibit 15 NR1A/2B NMDA Receptor Activation (FLIPR Assay)**

The activity of selected compounds to inhibit NR1A/2B NMDA receptor activation measured as NR1A/2B receptor-mediated  $\text{Ca}^{2+}$  influx is assessed by the following procedure:

20 NR1A/2B receptor transfected L(tk) cells are plated in 96-well format at  $3 \times 10^6$  cells per plate and grown for one - two days in normal growth media (Dulbeccos MEM with Na pyruvate, 4500 mgglucose, pen/strep, glutamine, 10% FCS and 0.5mg/ml genetin). NR1A/2B-expression in these cells is induced by the addition of 4nM dexamethasone in the presence of 500 $\mu\text{M}$  ketamine for 16 - 24 hours.  
25 After receptor induction cells are washed using a LabSystem Cellwisher two times with assay buffer (Hanks balanced salt solution (HBSS- $\text{Mg}^{++}$  free) containing 20mM HEPES, 0.1% BSA, 2mM  $\text{CaCl}_2$  and 250 $\mu\text{M}$  probenecid). The cells of each 96 well cell plate are loaded with the  $\text{Ca}^{++}$  sensitive dye Fluo-3 (Molecular Probes, Inc.) at 4 $\mu\text{M}$  in assay buffer containing 0.5% FBS, and 0.04% pluronic F-127 (Molecular  
30 Probes, Inc.) for 1h at 37 °C avoiding light. The cells are then washed with the Cellwisher four times with assay buffer leaving them in 100 $\mu\text{l}$  buffer. Test compounds in solution are pipetted by FLIPR (Fluorometric Imaging Plate Reader) into each test well for a 2min pretreatment. During this time the fluorescence intensity is recorded (excitation at 488nm and emission at 530nm). The  
35 glutamate/glycine 50 $\mu\text{L}$  agonist solution (final concentration 1 $\mu\text{M}$ /1 $\mu\text{M}$ ) is then added

by FLIPR into each well already containing 150 $\mu$ L of buffer (containing the test compound or vehicle) and the fluorescence is continuously monitored for 10min. The endpoint fluorescence values are used to determine an IC<sub>50</sub> value comparing the agonist-stimulated signal for the vehicle alone sample and that for the cells incubated 5 with each concentration of test compound.

Determining the Apparent Dissociation Constant (Ki) of Compounds  
for Human NR1A/NR2B Receptors (Binding Assay):

10

The radioligand binding assay is performed at room temperature in 96-well microtiter plates with a final assay volume of 1.0mL in 20mM Hepes buffer (pH 7.4) containing 150mM NaCl. Solutions of test compounds were prepared in DMSO and serially diluted with DMSO to yield 20 $\mu$ L of each of 10 solutions differing by 3-fold 15 in concentration. Non-specific binding (NSB) using hot AMD-1 (10 $\mu$ M final concentration) and total binding (TB) by using DMSO (2% final concentration). A solution of NR1A/NR2B receptors (40pM final concentration) and tritiated AMD-2 (1nM final concentration) were added to the test compounds. After 3h of incubation at room temperature, samples are filtered through Packard GF/B filters (presoaked in 20 0.05% PEI, polyethyleninone Sigma P-3143) and washed 10 times with 1mL of cold 20mM Hepes buffer per wash. After vacuum drying of the filter plates, 40 $\mu$ L of Packard Microscint-20 was added and bound radioactivity determined in a Packard 25 TopCount. The apparent dissociation constant (Ki), the maximum percentage inhibition (%I<sub>max</sub>), the minimum percentage inhibition (%I<sub>min</sub>) and the hill slope (nH) were determined by a non-linear least squares fitting the bound CPM data to Equation #1 below.

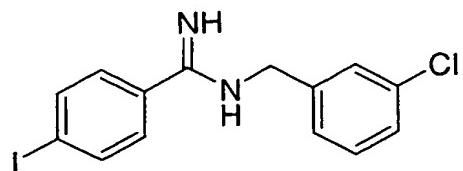
Equation#1:

30

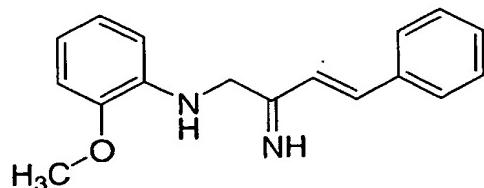
$$\text{CPM Bound} = \frac{(\text{SB}) (\%I_{\text{max}} - \%I_{\text{min}})}{(1 + (([\text{Drug}] / (K_i [L-844,345]/K_D))^{nH}))} + \text{NSB} + (\text{SB}) (1 - \%I_{\text{max}})$$

where,  $K_D$  is the apparent dissociation constant for the radioligand for the receptor as determined by hot saturation and SB is the specifically bound CPM determined from the difference of TB and NSB.

5 AMD-1

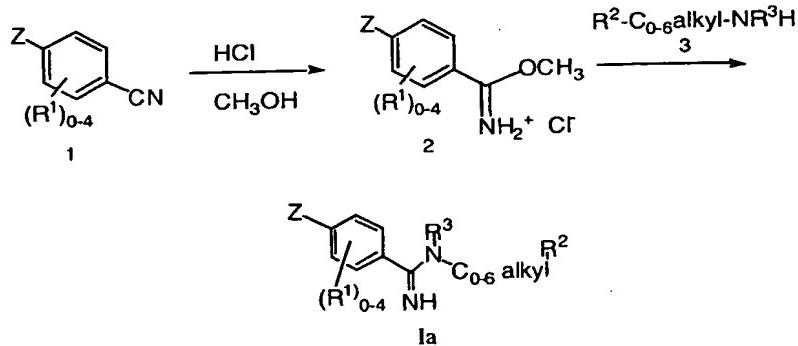


AMD-2



10 Compounds AMD-1 and AMD-2 can be synthesized in accordance with the following general reaction schemes.

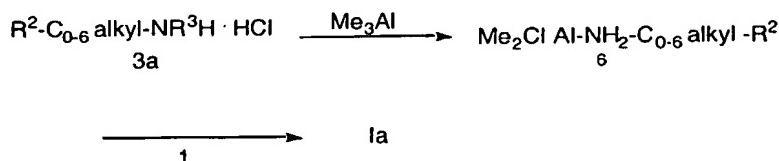
SCHEME 1



15 In accordance with scheme 1, hydrogen chloride is bubbled through a solution of the appropriately substituted benzonitrile 1 in methanol at room temperature. The volatiles are removed under reduced pressure and the resulting

residue is triturated with ether and filtered to yield the desired imidate 2. Imidate 2 is dissolved in methanol at ambient temperature, treated with amine 3 at ambient temperature and stirred under argon. The volatiles are removed under reduced pressure and the residue purified by preparative HPLC or trituration with ether to afford amidine Ia.

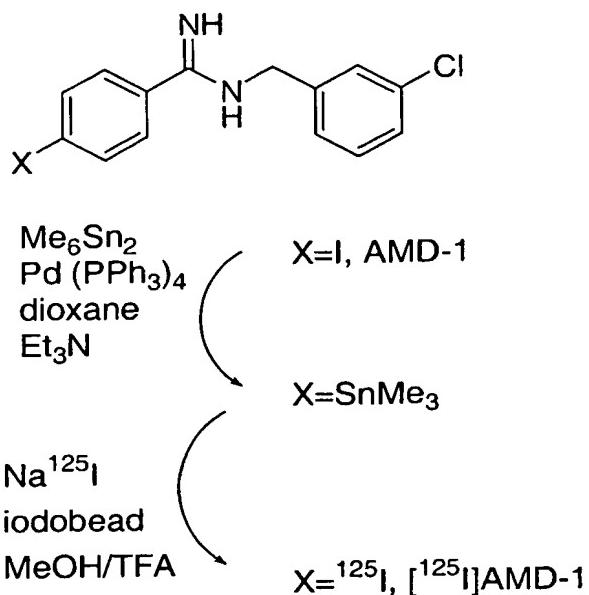
## SCHEME 2



In accordance with scheme 2, at room temperature under argon, amine 10 3a is dissolved in ether and was treated with 1-M hydrogen chloride in ether (1 equiv.) in a single portion. The resulting precipitate is stirred vigorously for 10 minutes. The volatiles are removed under reduced pressure. The residue is suspended in toluene, cooled to 0°C under argon, treated with 2.0-M trimethylaluminum (1.05 equiv.) in a dropwise manner, and stirred for 45 minutes at room temperature to afford 15 intermediate 6 (not isolated). Compound 6 is added to a solution of nitrile 1 in toluene. The reaction is heated to 80°C without stirring in a sealed tube for 18h, cooled to ambient temperature, poured onto a silica gel column and eluted with methanol/dichloromethane to give the amidine 4.

20

Preparation of [<sup>125</sup>I]AMD-1



Tritiated AMD-1 was prepared by the following procedure: A mixture of AMD-1, hydrochloride salt, (5mg, 0.012mmol) in dioxane (0.2mL) containing triethylamine (4µL) was treated with hexamethylditin (5µL), a catalytic amount of palladium catalyst and heated at 100°C for 45 minutes. The reaction was cooled to room temperature, filtered through a glass wool plug, rinsed with methanol and concentrated *in vacuo* to give 10.7mg of a brown oil. The oil was dissolved in methylene chloride and passed through a small silica column eluting with methylene chloride followed by 5% methanol/methylene chloride. Fractions containing the trimethylstannane (*R*<sub>f</sub> 0.26 in 10% methanol/methylene chloride) were pooled and concentrated *in vacuo* to give 4.5mg of the trimethylstannane as a clear colorless oil. This material was further purified by HPLC (C18 Econosil, 10x250mm, 20 minute linear gradient, 30% MeCN:70% H<sub>2</sub>O (0.1% TFA) to 90% MeCN, 3mL/min, 254nm, retention time 15 minutes) to give 3mg of the trimethylstannane.

A Na<sup>125</sup>I shipping vial (10mCi, Amersham) was charged with a stir bar, an iodobead, 50µL of methanol and stirred five minutes at room temperature. A solution of the trimethylstannane (0.1mg) in 50µL of methanol containing 5µL of trifluoroacetic acid was added and the reaction was stirred for five minutes. The reaction was quenched with 50µL of ammonium hydroxide and purified by HPLC (C18 Vydac protein and peptide column, 4.6 x 250 mm, 20 minute linear gradient,

30% MeCN:70% H<sub>2</sub>O (0.1% TFA) to 90% MeCN, 1mL/min, retention time 11minutes). Fractions containing the radioactive product were pooled and concentrated *in vacuo* to give 989μCi of [<sup>125</sup>I]AMD-1 with a specific activity of 898Ci/mmol as measured by UV absorbance at 272nm.

5

### Synthesis of Tritiated AMD-2

Tritiated AMD-2 was prepared by the following procedure: The phenol of AMD-2 (2mg, 0.008mmol) dissolved in dimethylformamide (0.6mL) and potassium carbonate (1.2mg) for 1hr. High specific activity tritiated methyl iodide (50mCi, 0.0006mmol, in toluene 1mL, American Radiolabeled Chemicals) was added at room temperature and stirred for 2 hours. The reaction mixture was filtered using a Whatman PTFE 0.45μm syringeless filter device to remove any insoluble potassium carbonate, washed with Abs. ethanol (2mL, Pharmco), and the combined filtrates were concentrated to dryness at room temperature using a rotary evaporator; this also removed any unreacted tritiated methyl iodide. The residue was purified by HPLC chromatography on a Phenomenx Luna C8 semi-prep column (Luna 5 micro C8(2), 250x10.0 mm) using a gradient system of 20/80 acetonitrile/water with 0.1% trifluoroacetic acid to 100% acetonitrile with 0.1% trifluoroacetic acid in 20min. Total activity of the product was 8mCi. Further purification was effected by absorption onto a Waters C-18 Sep-pak column (Waters Sep-Pak PLUS C18) and elution with water followed by absolute ethanol. The product was diluted with absolute ethanol (10mL) before submission for final analysis.

The compounds of this invention exhibit less than 50μM in the FLIBR and binding assays. Thus, the compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as NMDA NR2B antagonists. Accordingly, another aspect of the invention is the treatment of pain, migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke – maladies that are amenable to amelioration through inhibition of NMDA NR2B receptors – by the administration of an effective amount of the compounds of this invention.

The following examples are provided to more fully illustrate the present invention, and are not to be construed as limiting the scope of the claims in any manner.

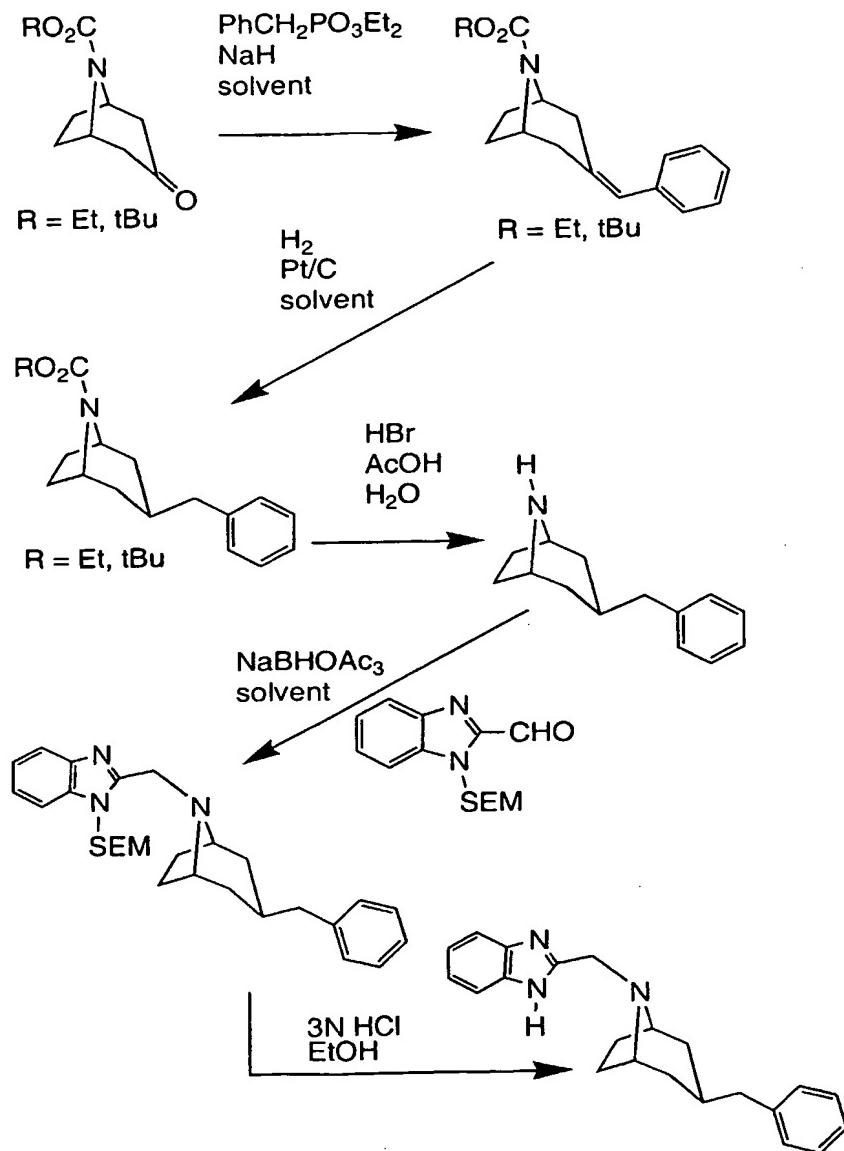
35

## EXAMPLES

Preparation of 8-substituted tropanes.

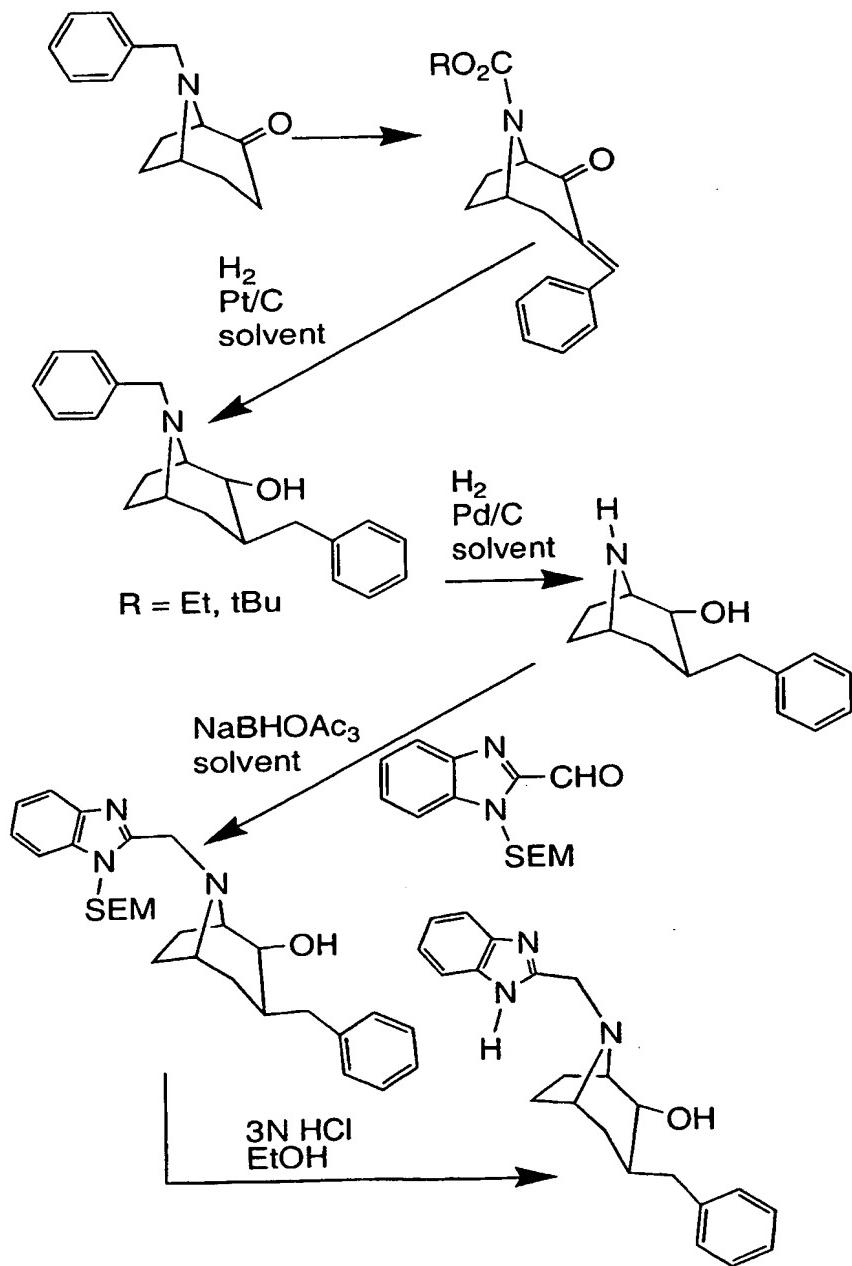
In one Example, 8-substituted tropanes were prepared by Scheme 1  
5 shown below:

Scheme 1

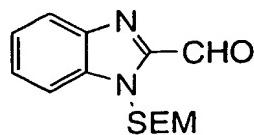


In another Example, 8-substituted tropanes were prepared by Scheme 2 shown below:

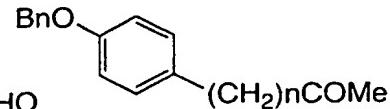
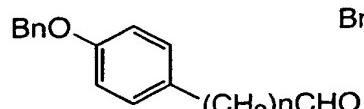
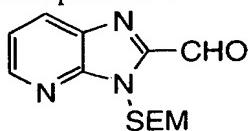
Scheme 2



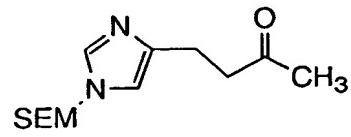
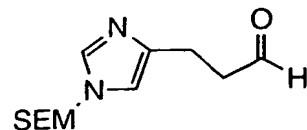
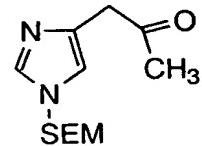
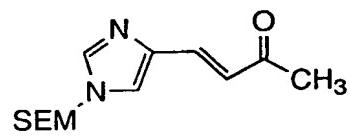
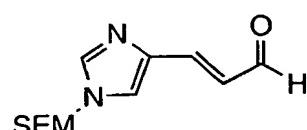
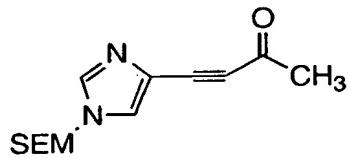
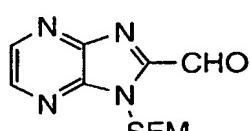
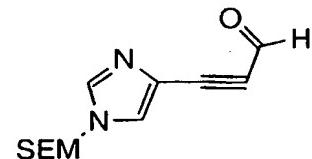
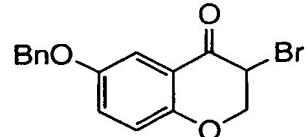
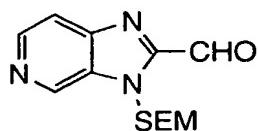
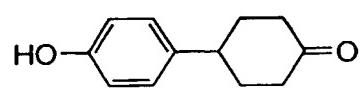
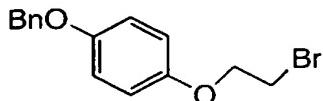
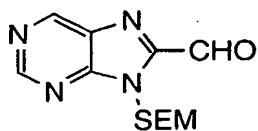
In Schemes 1 and 2 above, in place of the 1-SEM-benzimidole-2-carboxaldehyde

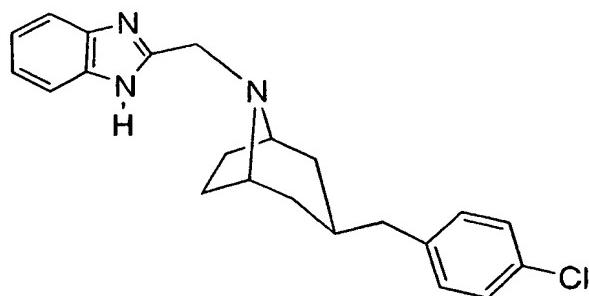


any of the following aldehydes, ketones, or bromides can be used to prepare the  
5 compounds of this invention:



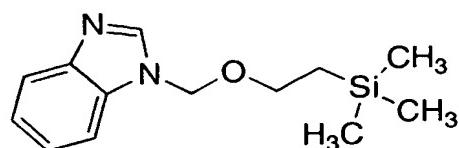
$n = 0, 1, 2, 3$



EXAMPLE 1**2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

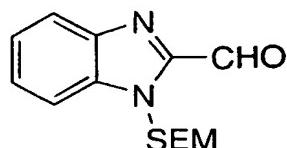
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Example 1 was prepared by the following procedure.

**Step 1:****1-(2-Trimethylsilylethoxymethyl)-1H-benzimidazole**

10

A mixture of KH, from 7g of 30% oil dispersion, and 5g of benzimidazole in 100mL of THF was stirred under nitrogen at room temperature for 18h. To the stirred suspension was added 7g of 2-trimethylsilylethoxymethyl chloride and the mixture kept at room temperature for 24h, cooled in an ice bath, cautiously quenched with 50mL of water, and extracted into ether. The combined ether extracts were dried over MgSO<sub>4</sub> and concentrated. Low pressure chromatography over silica gel eluting with a gradient of 3:1 ethyl acetate:hexane to 100% ethyl acetate gave 9.5g of 1-SEM-benzimidazole as a colorless oil.

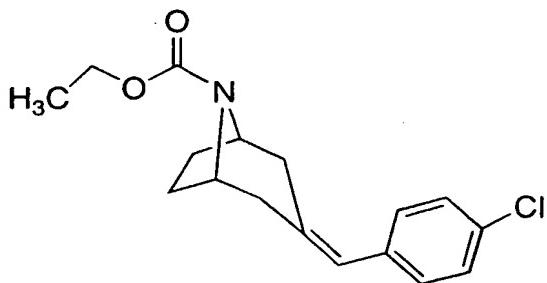
**Step 2:**

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**1-(2-Trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde**

To a solution of 40mmole of lithium diisopropylamide in 100mL of THF cooled to -78°C was added 5g of 1-SEM-benzimidazole in 50mL of THF. After 1.5h at or below -70°C, the red solution was quenched by rapid addition of 6mL of methyl formate. After warming to room temperature over 30min, 50mL of water and 200mL of ethyl acetate were added. The organic layer was separated and dried over MgSO<sub>4</sub> then concentrated under reduced pressure to 5.3g of a thick oil that solidified in the freezer.

10 **Step 3:**

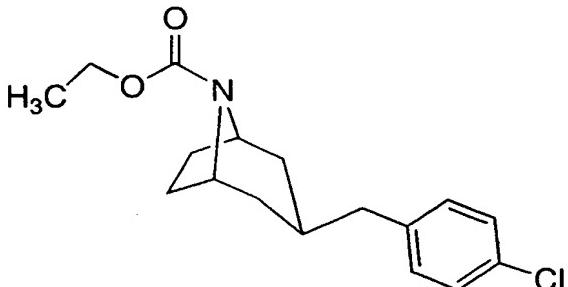


**3-(4-Chloro-benzylidene)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester**

To a stirred solution of 2g of N-carbethoxy-4-tropinone and 3.5g of diethyl 4-chlorobenzylphosphonate in 10mL of 1,3-dimethyl-2-imidazolidinone dried over 4Å mol sieves was added 0.50g of 60% NaH oil dispersion. The mixture was allowed to stir overnight, diluted with 200mL of water and extracted with 3X100mL of ether. Combined extracts were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Low pressure chromatography over silica gel eluting with a gradient of 5:95 ethyl acetate:hexane to 1:5 ethyl acetate:hexane gave 2g of olefin as a colorless oil.

20

**Step 4:**

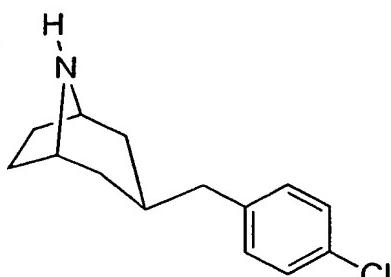


**3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester**

A solution of 2g of 3-(4-chloro-benzylidene)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 0.5g of 5% platinum on carbon in 100mL of ethanol was allowed to stir overnight under 1atm of hydrogen. The catalyst was filtered off and the solution concentrated to give 2g of a 2:1 mixture of exo:endo isomers of 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester as an oil.

**Step 5:**

10

**3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]octane**

A mixture of 2g of 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester, 20mL of 48% HBr and 5mL of acetic acid was heated to reflux for 2h. After cooling in an ice bath, the solution was basified to pH 10 by addition of NaOH pellets, extracted with 3X100mL of chloroform, and the combined extracts dried over MgSO<sub>4</sub>. Removal of solvents under reduced pressure gave 1.5g of 2:1 exo:endo 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane as a thick oil.

**Step 6:****2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

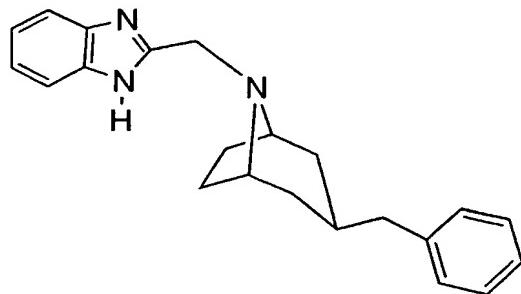
A mixture of 0.5g of 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane, 0.5g of 1-(2-trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde, 5mL of 1,2-dichloroethane and 0.5g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude SEM ether was heated to reflux in 50mL of ethanol containing 5mL of 3N HCl for 2h,

cooled, concentrated and partitioned between 10ml of saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and 3X25mL of chloroform. The chloroform extracts were dried over MgSO<sub>4</sub> and concentrated. Purification by chromatography eluting with 90:10 CHCl<sub>3</sub>:MeOH gave 0.75g of 2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole as a 2:1 mixture of exo:endo isomers. Chromatography on a Chiralpak™ AS column eluting with a 90:10 mixture of hexane with 0.10% diethylamine and isopropanol gave 0.25g of endo 2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT = 5.34min; MS (m+1) = 366; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 3.8 (s, 2H), 3.2 (s, 2H), 2.75 (d, 2H), 2.05 (m, 2H), 1.8 (d, 2H).

Later fractions gave 0.5g of exo 2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT = 9min; MS (m+1) = 366; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 9.75 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m, 4H), 7.1 (d, 1H), 3.8 (s, 2H), 3.2 (s, 2H), 2.5 (d, 2H), 2.0 (m, 2H), 1.9 (m, 2H).

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### EXAMPLE 2



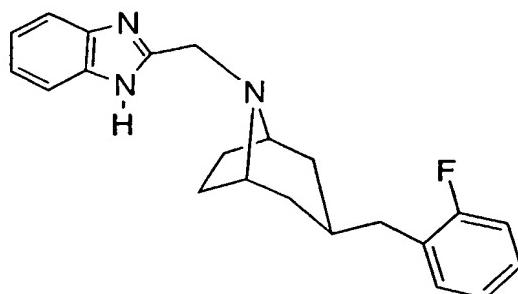
#### **2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole**

Example 2 was prepared by following the procedures described above for Example 1, but substituting diethyl benzylphosphonate for diethyl 4-chlorophosphonate. Chromatography on a Chiralpak™ AD column eluting with a 90:10 mixture of hexane with 0.10% diethylamine and isopropanol yielded exo 2-[3-benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT 4.6min; MS (m+1) = 332.4; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m, 7H), 3.8 (s, 2H), 3.2 (s, 2H), 2.55 (d, 2H), 2.05 (m, 2H), 1.6 (d, 2H), 1.5 (m, 3H), 1.2 (m, 2H).

Later fractions gave endo 2-[3-benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT = 6.2min; MS (m+1) = 332.4; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m, 7H), 3.8 (s, 2H), 3.2 (s, 2H), 2.75 (d, 2H), 2.1 (m, 5H), 1.85 (m, 2H), 1.4 (d, 2H).

5

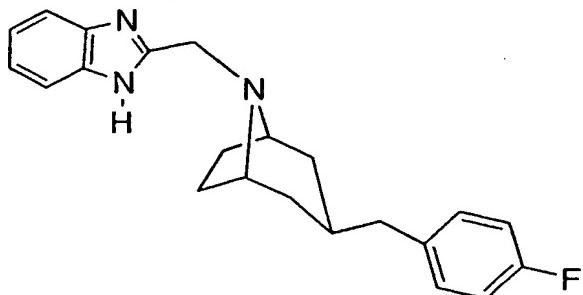
### EXAMPLE 3



#### **2-[3-(2-Fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

10 Example 3 was prepared by following the procedures described above for Example 1, but substituting diethyl 2-fluorobenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(2-fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 350; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.6 (br, 2H), 7.5 (br, 1H), 7.2 (m, 4H), 15 6.9 (m, 2H), 3.9 (s, 2H), 3.25 (s, 2H), 2.8 (d, 0.6 x 2H, endo), 2.55 (d, 0.4 x 2H, exo), 2.2 (m, 4H), 1.9 (d, 2H), 1.7-1.4 (m, 3H).

### EXAMPLE 4



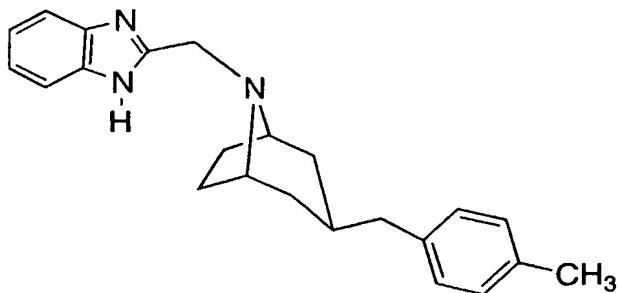
20

**2-[3-(4-Fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

Example 4 was prepared by following the procedures described above for Example 1, but substituting diethyl 4-fluorobenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography on a Chiralpak™ AD column eluting with a 5 90:10 mixture of hexane with 0.10% diethylamine and isopropanol yielded exo 2-[3-(4-fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 350; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m, 7H), 3.8 (s, 2H), 3.2 (s, 2H), 2.55 (d, 2H), 2.05 (m, 2H), 1.6 (d, 2H), 1.5 (m, 3H), 1.2 (m, 2H).

10 Later fractions gave endo 2-[3-(4-fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 350 ; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.8 (br, 1H), 7.45 (br, 1H), 7.25 (m, 2H), 7.15 (m, 2H), 6.95 (m, 2H), 3.82 (s, 2H), 3.2 (s, 2H), 2.70 (d, 2H).

15

**EXAMPLE 5****2-[3-(4-Methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

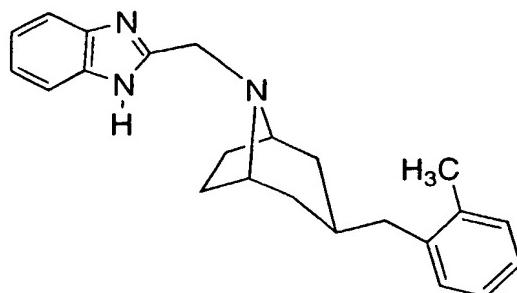
Example 5 was prepared by following the procedures described above for Example 1, but substituting diethyl 4-methylbenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography on a Chiralpak™ column eluting with a 90:10 mixture of hexane with 0.10% diethylamine and isopropanol gave endo 2-[3-(4-methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT 17.04min; MS (m+1) = 346 ; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 25 7.2 (m, 6H), 3.8 (s, 2H), 3.2 (s, 2H), 2.7 (d, 2H), 2.3 (s, 3H).

Later fractions gave endo 2-[3-(4-methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT = 20.4min; MS (m+1) = 346;

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.7 (br, 1H), 7.5 (br, 1H), 7.2 (m, 4H), 7.1 (dd, 2H), 3.85 (s, 2H), 3.2 (s, 2H), 2.5 (d, 2H), 2.35 (s, 3H), 2.05 (m, 2H), 1.85 (m, 2H), 1.8-1.6 (m, 4H), 1.48 (m, 1H).

5

EXAMPLE 6

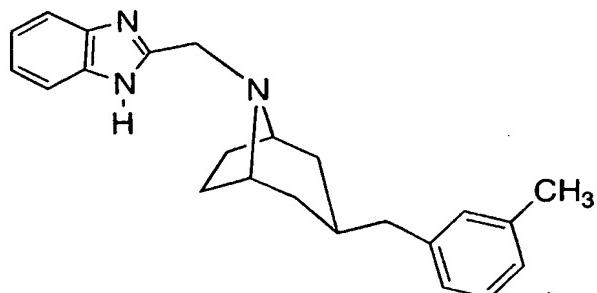


**2-[3-(2-Methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

Example 6 was prepared by following the procedures described above for Example 1, but substituting diethyl 2-methylbenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(2-methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 346; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.6 (br, 2H), 7.5 (br, 1H), 7.2 (m, 5H), 3.95 (s, 2H), 3.30 (br s, 2H), 2.86 (d, 2H), 2.40 (s, 3H).

15

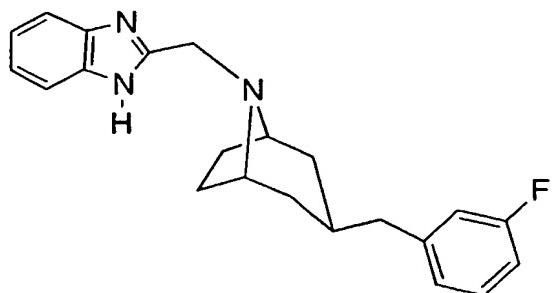
EXAMPLE 7



**2-[3-(3-Methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

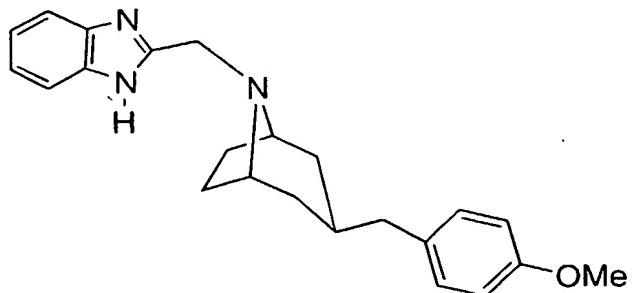
Example 7 was prepared following the procedures described above for Example 1, but substituting diethyl 3-methylbenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(3-methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 346.5; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.6 (br, 2H), 7.5 (br, 1H), 7.2 (m, 4H), 6.9 (m, 2H), 3.9 (s, 2H), 3.25 (s, 2H), 2.7 (d, 0.6 x 2H, endo), 2.5 (d, 0.4 x 2H, exo), 2.3 (2s, 3H), 2.2 (m, 4H), 1.9 (d, 2H), 1.7-1.4 (m, 3H).

10

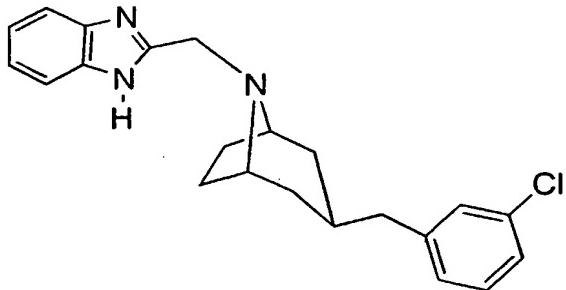
EXAMPLE 8**2-[3-(3-Fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

Example 8 was prepared following the procedures described above for Example 1, but substituting diethyl 3-fluorobenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(3-fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 350 ; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.6 (br, 1H), 7.5 (br, 1H), 7.2 (m, 4H), 6.9 (m, 2H), 3.85 (m, 2H), 3.25 (br s, 2H), 2.75 (d, 0.6 x 2H, endo), 2.5 (d, 0.4 x 2H, exo).

15  
20

EXAMPLE 9**2-[3-(4-Methoxy-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

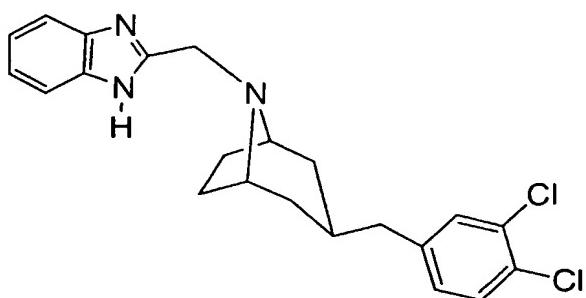
Example 9 was prepared by following the procedures described above for Example 1, but substituting diethyl 4-methoxybenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(4-methoxy-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 362; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.6 (br, 1H), 7.5 (br, 1H), 7.2 (m, 4H), 7.0 (m, 2H), 3.80 (m, 2H), 3.2 (br s, 2H), 2.7 (d, 0.6 x 2H, endo), 2.52 (d, 0.4 x 2H, exo) 2.35 (s, 3H).

EXAMPLE 10**2-[3-(3-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

Example 10 was prepared by following the procedures described for Example 1, but substituting diethyl 3-chlorobenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(3-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS (m+1) = 366; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 10 (br, 1H), 7.6 (br, 1H), 7.5 (br, 1H), 7.2 (m, 4H),

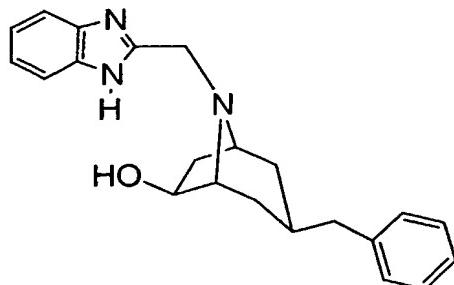
7.0 (m, 2H), 3.80 (m, 2H), 3.2 (br s, 2H), 2.75 (d, 0.6 x 2H, endo), 2.5 (d, 0.4 x 2H, exo).

5.

EXAMPLE 11**2-[3-(3,4-Dichloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole**

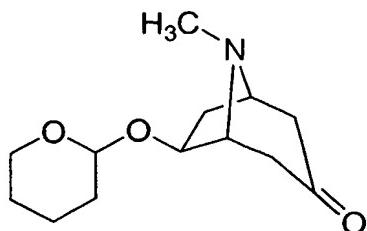
Example 11 was prepared following the procedures described for Example 1, but substituting diethyl 3,4-dichlorobenzylphosphonate for diethyl 4-chlorophosphonate. Chromatography yielded a mixture of exo and endo 2-[3-(3,4-dichloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: MS ( $m+1$ ) = 400;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 10 (br, 1H), 7.6 (br, 1H), 7.5 (br, 1H), 7.2 (m, 3H), 7.0 (m, 2H), 3.80 (m, 2H), 3.2 (br s, 2H), 2.70 (d, 0.6 x 2H, endo), 2.5 (d, 0.4 x 2H, exo).

15

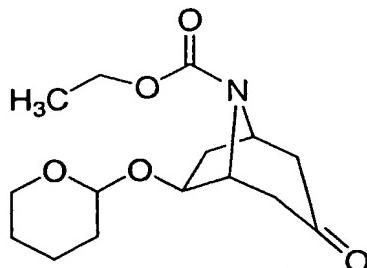
EXAMPLE 12**8-(1H-Benzimidazol-2-ylmethyl)-3-benzyl-8-aza-bicyclo[3.2.1]octan-6-ol**

20

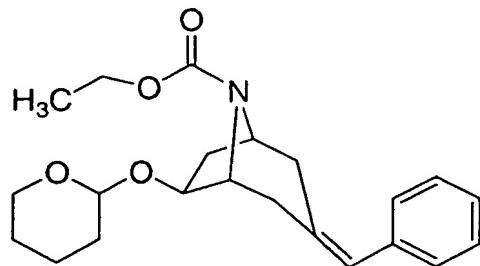
Example 12 was prepared by the following procedure.

**Step 1:****8-Methyl-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octan-3-one:**

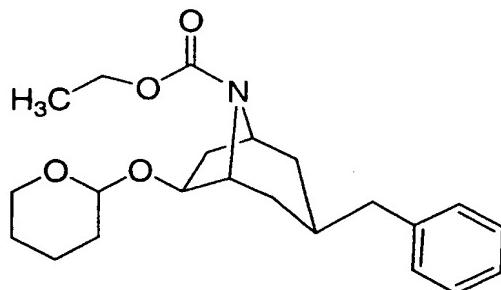
- A mixture of 1g of exo-6-hydroxytropinone, 50mL of methylene chloride and 3g of dihydropyran was stirred for 3 days. The mixture was diluted with 100mL of methylene chloride and washed with 50mL of 1N NaOH. Purification of the residue after concentration by chromatography eluting with a gradient of 190:10:1 to 180:20:5 EtOAc:MeOH:Et<sub>3</sub>N gave 1.6g of the THP-ether.

**10 Step 2:****3-Oxo-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester:**

- A mixture of 0.5g of 8-methyl-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octan-3-one, 1mL of ethyl chloroformate, 25mg of potassium carbonate, and 10mL of toluene was heated to reflux overnight. After cooling the mixture was diluted with 500mL of ether and 50mL of 3N NaOH and stirred for 2 hours. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. Drying under vacuum gave 0.60g of the ethyl carbamate.

**Step 3:****3-Benzylidene-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester:**

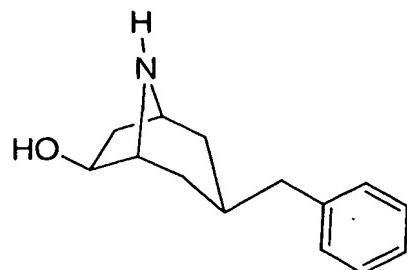
5            Olefination of 3-oxo-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester with diethyl phosphonate similarly to the procedure described previously in Step 3 of Example 1, gave 0.3g of a resin.

**Step 4:**

10

**3-Benzyl-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester:**

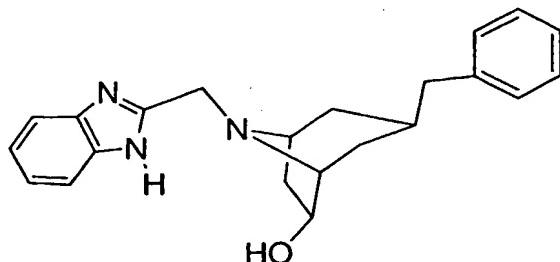
15            Hydrogenation of the 3-benzylidene-6-(tetrahydro-pyran-2-yloxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester similarly to the procedure described in Step 4 of Example 1 over 5% platinum on carbon gave 0.3g of a resin.

**Step 5:****3-Benzyl-8-aza-bicyclo[3.2.1]octan-6-ol:**

- A solution of the 3-benzyl-6-(tetrahydro-pyran-2-yloxy)-8-aza-  
 5 bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 0.5mL of trimethylsilyl iodide  
 in 25mL of chloroform was kept at room temperature for 48h, shaken with 25mL of  
 6N NaOH and dilute sodium sulfite and dried over magnesium sulfate. Removal of  
 solvents gave 0.2g of a resin.

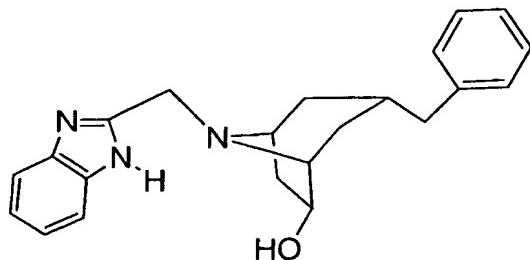
**10 Step 6:****8-(1H-Benzimidazol-2-ylmethyl)-3-benzyl-8-aza-bicyclo[3.2.1]octan-6-ol:**

- The 3-benzyl-8-aza-bicyclo[3.2.1]octan-6-ol was alkylated similarly to  
 the procedure as described for Step 6, Example 1. Separation of the diastereomeric  
 pair of enantiomers was performed on Chiralpak™ AD eluting with 95:5 0.1%  
 15 diethylamine in hexane:ethanol and gave in order of elution:



- 8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-  
 bicyclo[3.2.1]octan-6-ol enantiomer A: RT = 6.7min, MS (m + 1) = 348.4, <sup>1</sup>H NMR  
 (400MHz, CDCl<sub>3</sub>) 10.2 (br, 1H), 7.5 (br, 2H), 7.2 (m, 7H), 4.3 (dd, 1H), 4.2 (dd,  
 20 2H), 3.4 (d, 1H), 3.15 (s, 1H), 2.5 (d, 2H), 2.15 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H), 1.5  
 (m, 3H), 1.3 (m, 1H).

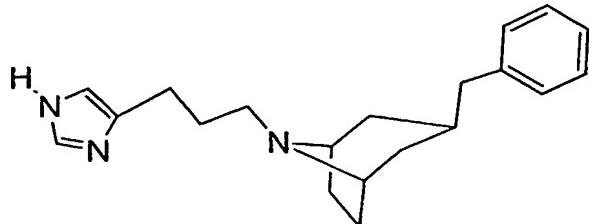
8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-  
 bicyclo[3.2.1]octan-6-ol enantiomer B: RT = 7.3min, MS (m + 1) = 348.4, <sup>1</sup>H NMR  
 (400MHz, CDCl<sub>3</sub>) 10.2 (br, 1H), 7.5 (br, 2H), 7.2 (m, 7H), 4.3 (dd, 1H), 4.2 (dd,  
 2H), 3.4 (d, 1H), 3.15 (s, 1H), 2.5 (d, 2H), 2.15 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H), 1.5  
 5 (m, 3H), 1.3 (m, 1H).



8-(1H-Benzimidazol-2-ylmethyl)-3-endo-benzyl-8-aza-  
 bicyclo[3.2.1]octan-6-ol enantiomer A: RT = 14.0min, MS (m + 1) = 348.4, <sup>1</sup>H NMR  
 10 (400MHz, CDCl<sub>3</sub>) 10.2 (br, 1H), 7.5 (br, 2H), 7.2 (m, 7H), 4.6 (dd, 1H), 4.25 (dd,  
 2H), 3.4 (s, 1H), 3.15 (s, 1H), 2.7 (d, 2H), 2.42 (dd, 1H), 2.1 (m, 4H), 1.3 (m, 2H).

8-(1H-Benzimidazol-2-ylmethyl)-3-endo-benzyl-8-aza-  
 bicyclo[3.2.1]octan-6-ol enantiomer B: RT = 15.3min, MS (m + 1) = 348.4, <sup>1</sup>H NMR  
 (400MHz, CDCl<sub>3</sub>) 10.2 (br, 1H), 7.5 (br, 2H), 7.2 (m, 7H), 4.6 (dd, 1H), 4.25 (dd,  
 15 2H), 3.4 (s, 1H), 3.15 (s, 1H), 2.7 (d, 2H), 2.42 (dd, 1H), 2.1 (m, 4H), 1.3 (m, 2H).

### EXAMPLE 13



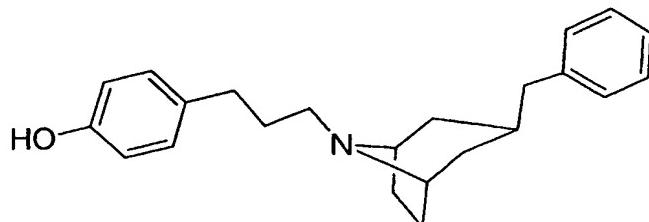
#### 20 3-Benzyl-8-[3-(1H-imidazol-4-yl)-propyl]-8-aza-bicyclo[3.2.1]octane

A mixture of 0.25g of 3-benzyl-8-aza-bicyclo[3.2.1]octane, 0.45g of 3-(1H-imidazol-4-yl)-propionaldehyde, 5mL of 1,2-dichloroethane and 0.5g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture

was diluted with 50mL chloroform and 10mL saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification by chromatography eluting with 90:10:1 CHCl<sub>3</sub>:MeOH:NH<sub>4</sub>OH gave 0.25g of 3-benzyl-8-[3-(1H-imidazol-4-yl)-propyl]-8-aza-bicyclo[3.2.1]octane as a 2:1 mixture of exo:endo isomers. MS (m+1) = 310.3; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 7.5-7.1 (complex, 6H), 6.75 (s, 1H), 3.22 (s, 2H), 2.75 (m, 2.6 H), 2.5 (d, 0.7 x 2H), 2.45 (m, 2H), 2.1 (m, 2H), 1.95 (m, 2H), 1.8 (m, 3H), 1.5 (m, 4H).

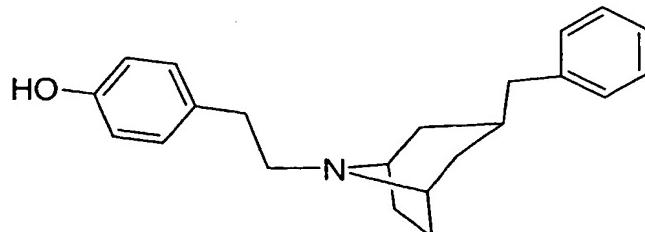
10

#### EXAMPLE 14



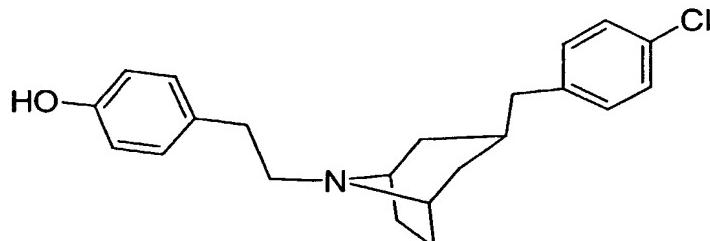
#### 4-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-phenol

15 A mixture of 0.18g of 3-benzyl-8-aza-bicyclo[3.2.1]octane, 0.30g of 3-(4-benzyloxy-phenyl)-propionaldehyde, 5mL of 1,2-dichloroethane and 0.3g of sodium triacetoxymethoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification by chromatography eluting with 80:20 EtOAc:MeOH gave 0.28g of 3-benzyl-8-[3-(4-benzyloxy-phenyl)-propyl]-8-aza-bicyclo[3.2.1]octane as a 2:1 mixture of exo:endo isomers. Hydrogenation at 1atm over 0.2g of 10% Pd/C in 50mL of ethanol gave 0.17g of 4-[3-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-phenol as a 2:1 mixture of exo:endo isomers: MS (m+1) = 336.4; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 7.25-7.1 (complex, 5H), 6.8 (d, 2H), 6.5 (d, 2H), 3.35 (br s, 2H), 2.75 (d, 0.6 H), 2.5-2.3 (complex, 5.4 H), 2.1 (m, 2H), 1.95 (m, 1H), 1.85 (m, 3H), 1.5 (m, 3H), 1.4 (m, 2H).

EXAMPLE 15**4-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-phenol**

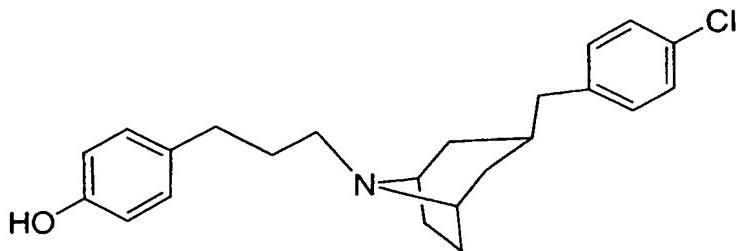
Example 15 was prepared in a similar manner to Example 14, 3-(4-benzyloxy-phenyl)-acetaldehyde, gave 4-[3-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-phenol as a 2:1 mixture of exo:endo isomers: MS ( $m+1$ ) = 323.2;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 7.3-7.15 (complex, 3H), 7.1 (d, 2H), 7.05 (d, 2H), 6.8 (d, 2H), 3.7 (br m, 2H), 3.0 (m, 2H), 2.95 (m, 3H), 2.6 (d, 0.65 x 2H), 2.4-1.2 (complex, 10).

10

EXAMPLE 16**4-{2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-phenol**

Example 16 was prepared in a similar manner to Example 15, 3-(1H-imidazol-4-yl)-acetaldehyde, gave 4-{2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-phenol as a 2:1 mixture of exo:endo isomers: MS ( $m+1$ ) = 356.2 ;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 7.3-6.95 (complex, 7H), 6.78 (d, 0.65 x 2H), 6.65 (d, 0.35 x 2H), 3.4 (br s, 2H), 2.8 (m, 4 H), 2.4-1.2 (complex, 10).

20

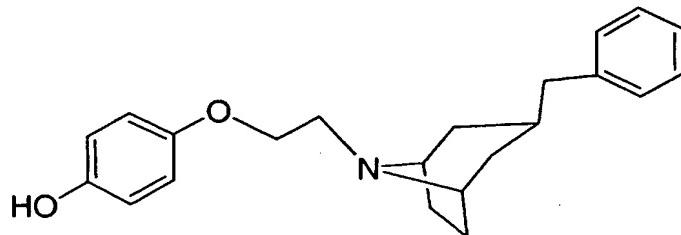
EXAMPLE 17**4-{3-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-propyl}-phenol**

Example 17 was prepared in a similar manner to Example 14, but substituting 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane for 3-benzyl-8-aza-bicyclo[3.2.1]octane gave 4-{3-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-propyl}-phenol as a 2:1 mixture of exo:endo isomers.

Separation by preparative TLC gave endo in the upper band: MS (m+1) = 370; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.3 (m, 2H), 7.05 (t, 2H), 6.85 (d, 2H), 6.6 (d, 2H), 3.7 (br s, 2H), 2.75 (d, 2H), 2.5 (dd, 2H), 1.7 (m, 2H), 1.55 (d, 2H).

The lower band contained the exo isomer: MS (m+1) = 370; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): 7.3 (m, 2H), 7.05 (t, 2H), 6.85 (d, 2H), 6.6 (d, 2H), 3.4 (br s, 2H), 2.75 (d, 1H), 2.5 (m, 4H), 2.1 (m, 2H), 1.9 (m, 4H), 1.7 (m, 2H), 1.55 (d, 2H), 1.4 (d, 2H).

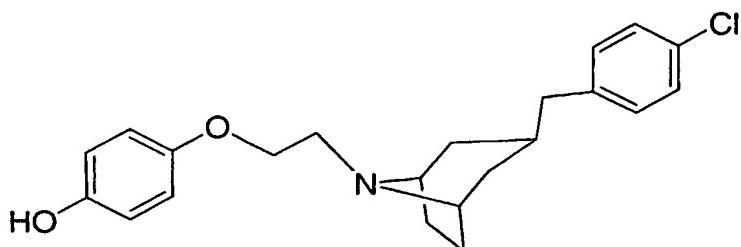
15

EXAMPLE 18**4-[2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-ethoxy]-phenol**

Example 18 was prepared by the following procedure. A mixture of 0.18g of 3-benzyl-8-aza-bicyclo[3.2.1]octane, 0.30g of 1-(2-Bromo-ethoxy)-4-benzyloxybenzene, 10mL of acetonitrile and 0.3g of potassium carbonate was stirred at reflux for 24 h. The reaction mixture was cooled, concentrated, diluted with 50mL

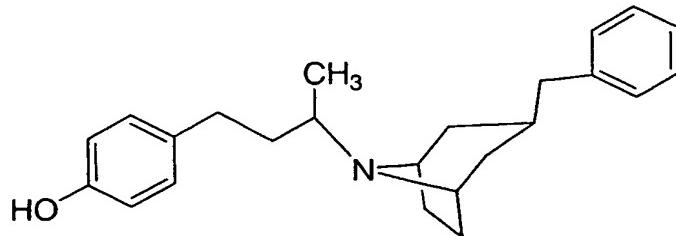
chloroform and 10mL saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and the layers separated. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Hydrogenation at 1atm over 0.2g of 10% Pd/C in 50mL of ethanol gave 0.17g of 4-[2-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-ethoxy]-phenol as a 2:1 mixture of exo:endo isomers after purification by chromatography eluting with 80:20 EtOAc:MeOH: MS (m+1) = 338.2; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 7.35-6.95 (complex, 5H), 6.76 (d, 2H), 6.6 (d, 2H), 4.1 (m, 2H), 3.5 (br s, 2H), 2.9 (m, 2 H), 2.8 (d, 0.3 x 2H), 2.54 (d, 0.7 x 2H), 2.2 (m, 1H), 1.95 (m, 2H), 1.75 (m, 4H), 1.5 (m, 2H).

10

EXAMPLE 19**4-{2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethoxy}-phenol**

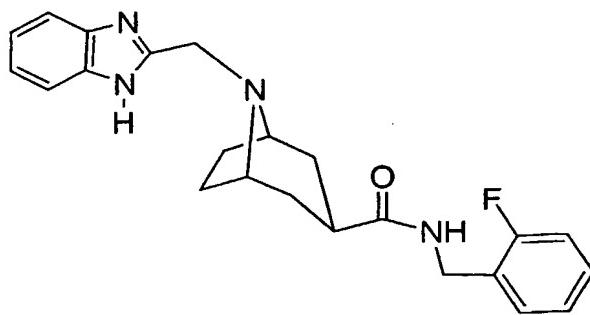
Example 19 was prepared in a similar manner to Example 18. 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane was substituted for 3-benzyl-8-aza-bicyclo[3.2.1]octane to yield 4-{2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethoxy}-phenol. Chromatography on a Chiralpak™ column first gave exo 4-{2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethoxy}-phenol: RT = 4.74min; MS (m+1) = 372; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 7.25 (d, 2H), 7.05 (d, 2H), 6.70 (s, 4H), 4.05 (t, 2H), 3.3 (br s, 4H), 2.75 (d, 2H), 2.45 (s, 2H), 1.95 (m, 2H), 1.8 (m, 1H), 1.5 (m, 1H).

Later fractions gave 0.5g of endo 4-{2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethoxy}-phenol: RT = 6.47min; MS (m+1) = 372; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 7.25 (d, 2H), 7.05 (d, 2H), 6.70 (s, 4H), 4.1 (t, 2H), 3.45 (br s, 4H), 2.95 (t, 2H), 2.8 (d, 2H), 1.90 (d, 2H).

EXAMPLE 20**4-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyl]-phenol**

Example 20 was prepared in a similar manner to Example 14.

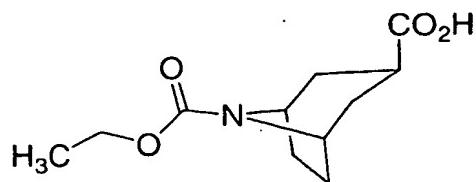
- 5 Substituting 4-(4-hydroxy-phenyl)-butan-2-one in place of 3-benzyl-8-aza-bicyclo[3.2.1]octane yielded 4-[3-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyl]-phenol as a 2:1 mixture of exo:endo isomers: MS ( $m+1$ ) = 350.5;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 7.35-7.2 (complex, 5H), 7.15 (dd, 2H), 6.94 (d, 1H), 6.82 (d, 1H), 3.8 (m, 2H), 3.5 (br s, 2H), 2.85 (m, 2 H), 2.85 (m, 2H), 2.54 (m, 2H), 2.4-2.0 (m, 1H), 1.5 (d, 2H), 1.0 (d, 3H), 1.8-1.1 (complex, 7H).
- 10

EXAMPLE 21

- 15 **8-(1H-Benzimidazol-2-ylmethyl)-8-aza-bicyclo[3.2.1]octane-3 -carboxylic acid 2-fluoro-benzylamide**

Example 21 was prepared by the following procedure.

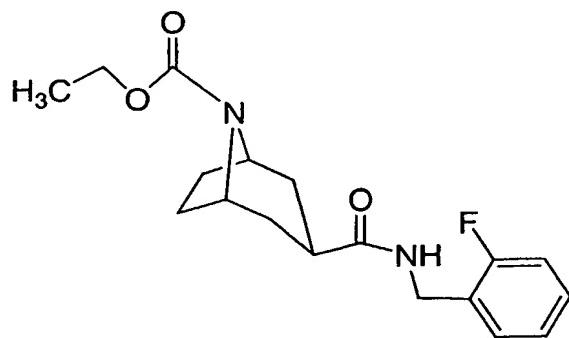
**Step 1:**



**8-Aza-bicyclo[3.2.1]octane-3,8-dicarboxylic acid 8-ethyl ester:**

- Following the general procedure described in U. Schöllkopf and R. Schröeder, *Angew. Chem. Int. Ed.*, **11**:311-312(1972), a solution of 2g of 1-isocyanomethanesulfonyl-4-methyl-benzene in 10mL of THF was added dropwise to an ice cooled suspension of 1.2g of potassium tert-butoxide in 20mL of THF. After cooling to -10°C, a solution of 1.7g of N-carbethoxytropinone in 10mL of THF was added over 5 min, and the solution stirred for 15 min at 0°C. The reaction was quenched with 0.6g of acetic acid and the solvent removed under reduced pressure.
- The residue was partitioned between 25mL of water and 50mL of methylene chloride, dried over magnesium sulfate and concentrated. The dark oily residue was refluxed in 20mL of 2N HCl for 12h, cooled, basified with 6N NaOH and washed with 25mL of ether. The aqueous layer was acidified to pH 1 with conc. HCl, extracted into 3X50mL of ether and the extracts dried over magnesium sulfate. Removal of solvents under reduced pressure gave 0.55g of an amber resin.

**Step 2:**



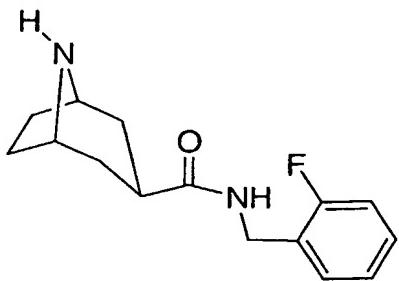
- 3-(2-Fluoro-benzylcarbamoyl)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester:**

A mixture of 100mg of 8-aza-bicyclo[3.2.1]octane-3,8-dicarboxylic acid 8-ethyl ester, 0.056g of HOBr, 0.074g of EDC, 0.073mL of triethylamine, 100mg of 2-fluorobenzylamine and 5mL of DMF was stirred at room temperature for 24h,

diluted with 50mL of 1N HCl and extracted into 3X25mL of ethyl acetate. The combined organic extracts were washed with 50mL of saturated sodium carbonate and dried over magnesium sulfate. Removal of solvents under reduced pressure gave 150mg of a resin.

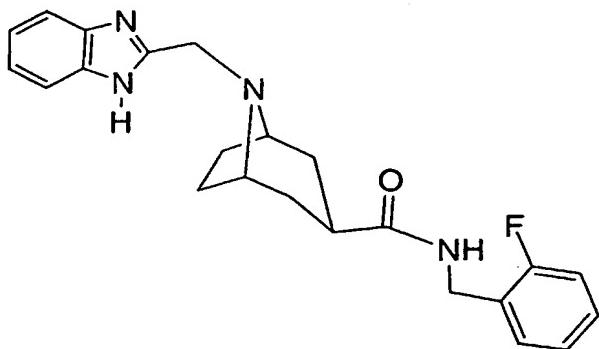
5

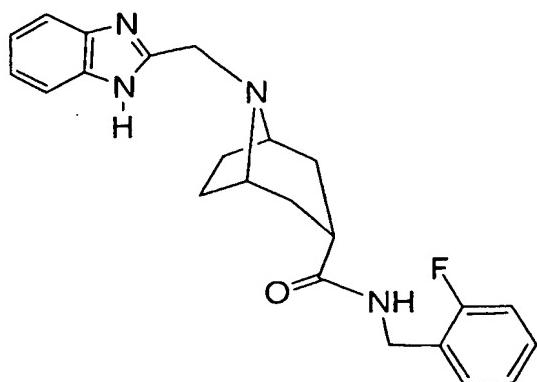
**Step 3:**



**8-Aza-bicyclo[3.2.1]octane-3-carboxylic acid 2-fluoro-benzylamide:**

- A solution of 0.15g of 3-(2-fluoro-benzylcarbamoyl)-8-aza-  
10 bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester and 0.5mL of trimethylsilyl iodide in 25mL of chloroform was kept at room temperature for 48h, shaken with 25mL of 6N NaOH and dilute sodium sulfite and dried over magnesium sulfate. Removal of solvents gave 0.09g of a resin.

15    **Step 4:**



**8-(1H-Benzimidazol-2-ylmethyl)-8-aza-bicyclo[3.2.1]octane-3-carboxylic acid 2-fluoro-benzylamide:**

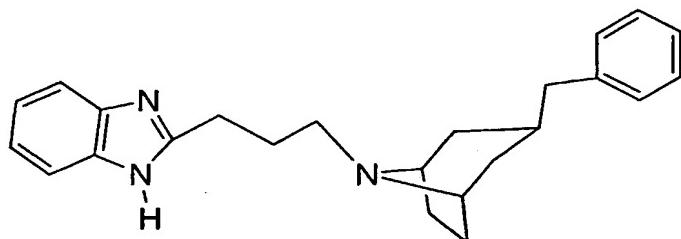
In a similar manner to Step 6, Example 1, reductive alkylation of 8-  
5 aza-bicyclo[3.2.1]octane-3-carboxylic acid 2-fluoro-benzylamide was performed with  
1-(2-trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde. After hydrolytic  
deprotection of the SEM protecting group, a mixture of exo and endo-8-(1H-  
benzimidazol-2-ylmethyl)-8-aza-bicyclo[3.2.1]octane-3-carboxylic acid 2-fluoro-  
benzylamide was obtained. The exo and endo forms were separated by preparative  
10 TLC eluting with 90:10 chloroform:methanol.

The faster moving band was the endo isomer: MS ( $m+1$ ) = 393.5;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 7.7 (br s, 1H), 7.5 (br s, 1H), 7.4-7.0 (complex, 6H), 5.9 (br, 1H), 4.5 (d, 2H), 3.8 (s, 2H), 3.3 (s, 2H), 2.5 (m, 1H), 2.1 (m, 4H), 1.6 (m, 3H).

The slower band was the exo isomer: MS ( $m+1$ ) = 393.5;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 7.7 (br s, 2H), 7.4-7.0 (complex, 6H), 5.9 (br, 1H), 4.5 (d, 2H), 3.9 (s, 2H), 3.15 (s, 2H), 2.6 (m, 1H), 2.3 (m, 2H), 2.1 (d, 2H), 2.0 (m, 2H), 1.9 (m, 2H).

20

**EXAMPLE 22**

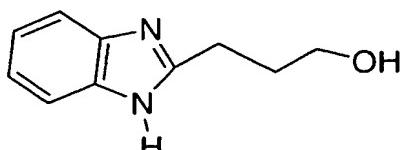


**2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-1H-benzimidazole**

Example 22 was prepared by the following procedure.

**Step 1:**

5

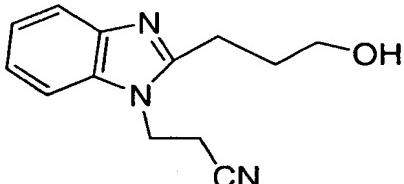


**3-(1H-Benzimidazol-2-yl)-propan-1-ol:**

A mixture of 5.4g of 1,2-phenylenediamine and 4.5g of dihydro-furan-2-one in 50mL of 4N hydrochloric acid was heated to reflux for 20h, 1 teaspoon of decolorizing carbon added, and after another 15 min reflux, filtered hot. The filtrate was concentrated under reduced pressure to near dryness, the residue made basic (pH = 8) with saturated sodium bicarbonate and extracted into 3X80mL of ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. After drying under vacuum, 8.4g of 3-(1H-benzimidazol-2-yl)-propan-1-ol was obtained as a solid.

15

**Step 2:**

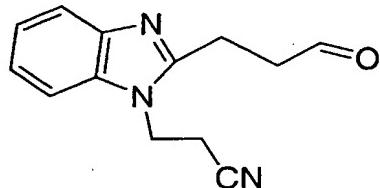


**3-[2-(3-Hydroxy-propyl)-benzimidazol-1-yl]-propionitrile:**

To a stirred solution of 3.8g of 3-(1H-benzimidazol-2-yl)-propan-1-ol and 4g dihydropyran in 500mL of THF was added p-toluenesulfonic acid monohydrate until the pH was about 3 (indicator paper). After stirring overnight, an additional 2mL of dihydropyran was added. After 2 additional hours, the conversion was complete. The mixture was concentrated under reduced pressure and partitioned between 250mL of 1N NaOH and 2X250mL of ether. After drying over magnesium sulfate the combined extracts were concentrated to dryness. To a solution of the resulting crude oily 2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-1H-benzimidazole (14g)

in 250mL of acetonitrile was added 5mL of acrylonitrile, 2 drops of 1M tetrabutylammonium fluoride in THF and 1 drop 10N NaOH. After heating to 85°C for 16h, conversion was complete (TLC elution with 90:10 methylene chloride:methanol). After concentration under reduced pressure, the residue was 5 partitioned between 2X200mL of ethyl acetate and 200mL of water. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. The crude 3-{2-[3-(tetrahydro-pyran-2-yloxy)-propyl]-benzimidazol-1-yl}-propionitrile was stirred in 250mL of methanol with sufficient p-toluenesulfonic acid monohydrate to make the solution acidic (pH = 1-2). After stirring overnight, the 10 solution was concentrated under reduced pressure, made basic (pH = 8) with 1N sodium hydroxide and extracted into 8X50mL of ethyl acetate. The aqueous layer was saturated with NaCl to aid in extraction of the product. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography using a gradient of ethyl acetate, then 10% methanol in ethyl acetate, 15 followed by trituration with ether-hexane gave 4.8g of 3-[2-(3-hydroxy-propyl)-benzimidazol-1-yl]-propionitrile as a solid.

**Step 3:**



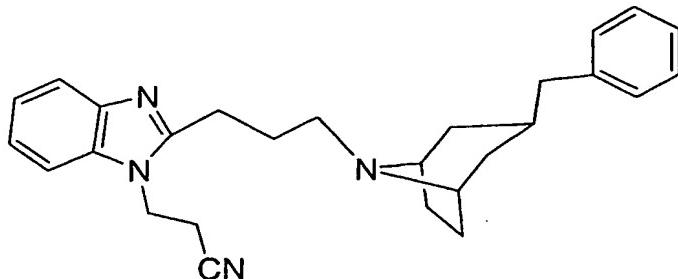
20 **3-[2-(3-Oxo-propyl)-benimidazol-1-yl]-propionitrile:**

To a stirred solution of 0.5g of oxalyl chloride in 15mL of methylene chloride cooled to -78°C was added 1mL of anhydrous DMSO. After 15 min, a solution of 1g of 3-[2-(3-hydroxy-propyl)-benzimidazol-1-yl]-propionitrile in 50mL of methylene chloride and 10mL of anhydrous DMSO was added while keeping the 25 temperature below -50°C. There was considerable precipitate which redissolved on warming to 0°C over 20 min. After cooling back down to -50°C, 5mL of triethyl amine was added and the mixture allowed to warm to room temperature. After 15min, the mixture was diluted with 250mL of water, shaken and separated. The organic layer was dried over magnesium sulfate and concentrated under reduced 30 pressure. The crude 3-[2-(3-oxo-propyl)-benimidazol-1-yl]-propionitrile was an

amber resin (1g), and contained only traces of the starting alcohol by TLC (90:10 methylene chloride:methanol).

**Step 4:**

5

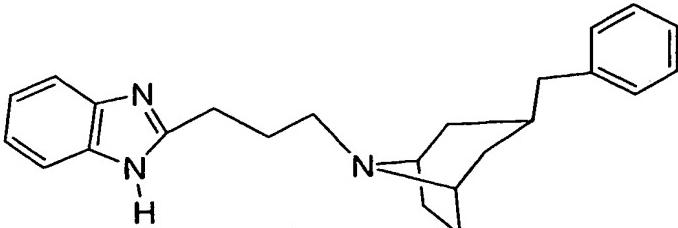


**3-{2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-benzimidazol-1-yl}-propionitrile:**

A mixture of 0.25g of 3-benzyl-8-aza-bicyclo[3.2.1]octane, 0.4g of 1-3-[2-(3-oxo-propyl)-benimidazol-1-yl]-propionitrile, 5mL of 1,2-dichloroethane and 10 0.3g of sodium triacetoxyborohydride was stirred at room temperature for 24 h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Low pressure chromatography eluting with a 15 gradient of 70:30 ethyl acetate:methanol to 70:30:5 ethyl acetate:methanol:triethylamine gave 400mg of pure 3-{2-[3-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-benzimidazol-1-yl}-propionitrile as a gum.

**Step 5:**

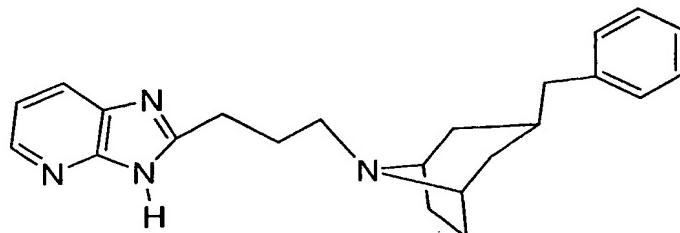
20



**2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-1H-benzimidazole:**

A mixture of 0.4g of 3-{2-[3-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-benzimidazol-1-yl}-propionitrile, 20mL of isopropanol and 2mL of 0.4M sodium in isopropanol was heated to reflux for 2h. Conversion was complete by TLC (80:20:1 ethyl acetate:methanol:triethylamine). The mixture was cooled, diluted with 5 10mL of saturated sodium bicarbonate and concentrated. The residue was partitioned between 3X100mL of chloroform and 50mL of water. After drying over magnesium sulfate and concentration under reduced pressure, the residue was purified by preparative TLC eluting with 400:100:25 ethyl acetate:methanol:triethylamine. The major band (UV visualization) was 2-[3-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-1H-benzimidazole (258mg): MS ( $m+1$ ) = 362.5;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 10 7.58 (d, 1H), 7.52 (d, 1H), 7.6-7.2 (complex, 7H), 3.38 (s, 2H), 3.18 (m, 2H), 2.82 (m, 2H), 2.6 (m, 2H), 2.22 (m, 2H), 2.1 (m, 2H), 1.85 (m, 5H), 1.6 (m, 2H).

### EXAMPLE 23

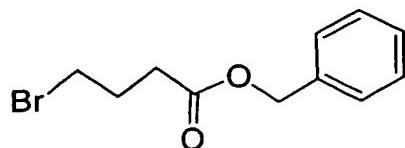


15

### **2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-3H-imidazo[4,5-b]pyridine**

Example 23 was prepared by the following procedure.

#### **Step 1:**



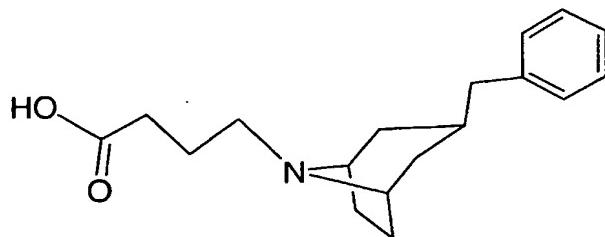
20

#### **4-Bromo-butyric acid benzyl ester**

To an ice cold solution of 5g of 4-bromobutyric acid and 5.5g of benzylchloroformate in 100mL of dichloromethane was added 5mL of triethylamine and then 700mg of 4-dimethylaminopyridine. A vigorous exothermic reaction ensued 25 with evolution of carbon dioxide. After stirring for 3h, the mixture was diluted with

100mL of dichloromethane and washed with 200mL of saturated sodium bicarbonate, dried over magnesium sulfate, and concentrated to an oil. Azeotropic drying with toluene gave 8g of 4-bromobutyric acid benzyl ester as a clear oil.

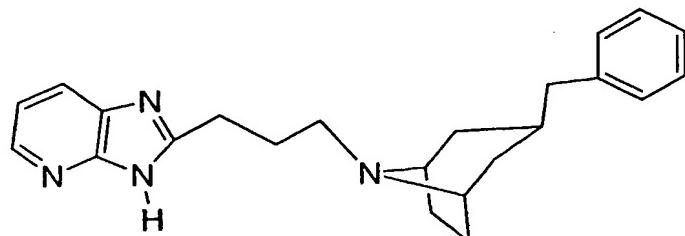
5    **Step 2:**



**4-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyric acid:**

A mixture of 0.9g of 4-bromobutyric acid benzyl ester, 0.5g of 3-benzyl-8-aza-bicyclo[3.2.1]octane, 0.6mL of N,N-diisopropylethylamine and 20mL of acetonitrile was heated to 80°C for 4h. The mixture was cooled, concentrated under reduced pressure and partitioned between chloroform and saturated sodium carbonate. After drying over magnesium sulfate the extracts were concentrated to a thick oil, 1.4g, which was a mixture of the benzyl ester of 4-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyric acid, benzyl 4-bromobutyrate, and butyrolactone. Hydrogenation over 10 0.5g of palladium on carbon in 100mL of ethanol under 1atm of hydrogen overnight gave 0.9g of 4-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyric acid after drying under 15 vacuum at 100°C overnight which was homogeneous by TLC (90:10:1 chloroform:methanol:ammonium hydroxide).

20    **Step 4:**

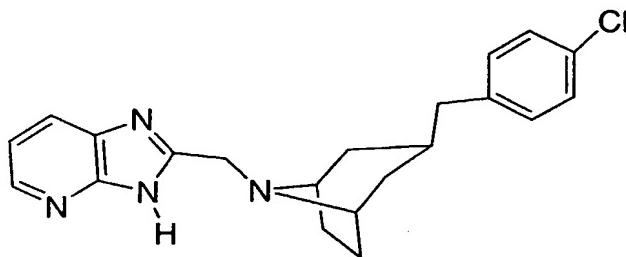


**2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-3H-imidazo[4,5-b]pyridine:**

A mixture of 0.6g of 4-(3-benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyric acid, 0.25g of 1,2-diaminopyridine and 6g of polyphosphoric acid was heated to 185°C for 2h. The mixture was cooled and stirred with 100mL of 3N sodium hydroxide for 1h after becoming homogeneous. The solution was extracted with 5 5X100mL of chloroform and the combined extracts washed 3X50mL of dilute ammonium hydroxide, heated with 1g of decolorizing carbon for 10min, cooled, filtered and concentrated. Purification of the residue by chromatography, eluting with 400:100:25 ethyl acetate:methanol:triethylamine gave 249mg of 2-[3-(3-benzyl-8-aza-10 bicyclo[3.2.1]oct-8-yl)-propyl]-3H-imidazo[4,5-b]pyridine: MS (m+1) = 363.5; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 8.38 and 8.3 (2 x d, 1H), 7.9 and 7.8 (2 x d, 1H), 7.4-7.1 (complex, 6H), 3.42 (s, 2H), 3.22 (m, 2H), 2.82 (m, 2H), 2.75 (m, 2H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 5H), 1.6 (m, 2H).

#### EXAMPLE 24

15

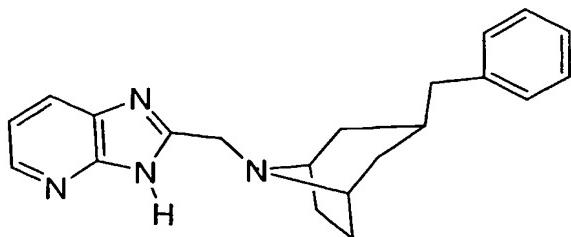


#### 2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-3H-imidazo[4,5-b]pyridine

Example 24 was prepared in a similar manner to Example 1, Steps 1-6, but substituting 3H-imidazo[4,5-b]pyridine for benzimidazole in Step 2.

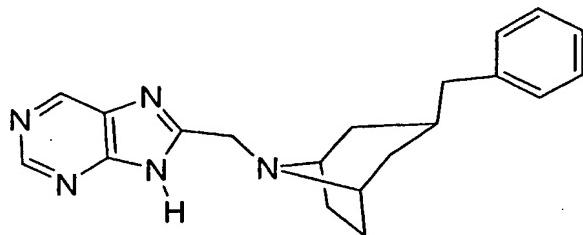
20 Chromatography on a Chiralpak™ gave endo 2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT = 17.1 min; MS (m+1) = 367; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 3.8 (s, 2H), 3.2 (s, 2H), 2.70 (d, 2H), 1.8 (d, 2H).

Later fractions gave exo 2-[3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole: RT = 9 min; MS (m+1) = 367; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 9.75 (br, 1H), 8.4 (d, 1H), 7.95 (d, 1H), 7.3-7.2 (m, 3H), 7.05 (d, 2H), 3.8 (s, 2H), 3.2 (s, 2H), 2.45 (d, 2H), 2.05 (d, 2H), 1.8 (m, 1H), 1.6 (d, 2H), 1.5 (m, 3H), 1.2 (m, 1H).

EXAMPLE 25**2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-3H-imidazo[4,5-b]pyridine**

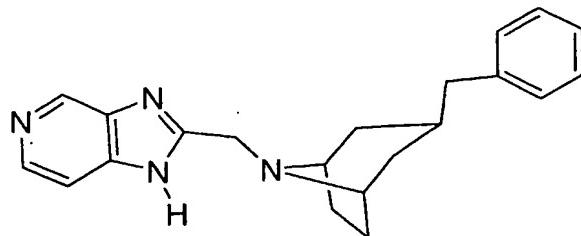
5 Example 25 was prepared in a similar manner to Example 24, but substituting 3-benzyl-8-aza-bicyclo[3.2.1]octane for 3-(4-chloro-benzyl)-8-aza-bicyclo[3.2.1]octane: MS ( $m+1$ ) = 333.5;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 9.75 (br, 1H), 8.4 (d, 1H), 7.95 (d, 1H), 7.4-7.05 (m, 6H), 3.9 (s, 2H), 3.22 (s, 2H), 2.78 (d, 0.65 x 2H), 2.55 (d, 0.35 x 2H), 2.18 (m, 4H), 2.05 (m, 1H), 1.9 (m, 1H), 1.6 (d, 1H), 1.5 (d, 2H), 1.4 (d, 1H).

10

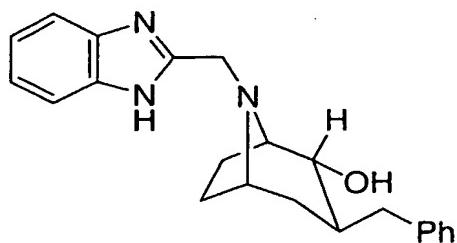
EXAMPLE 26**15 8-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-9H-purine**

Example 26 was prepared in a similar manner to Example 25, but substituting 9-(2-trimethylsilyl-ethoxymethyl)-9H-purine-8-carbaldehyde for 3-(2-trimethylsilyl-ethoxymethyl)-3H-imidazo[4,5-b]pyridine-2-carbaldehyde: MS ( $m+1$ ) = 335.5;  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ ) 9.02 (s, 1H), 8.95 (s, 1H), 7.3 -7.1 (m, 5H), 3.9 (s, 2H), 3.22 (s, 2H), 2.78 (d, 0.65 x 2H), 2.55 (d, 0.35 x 2H), 2.18 (m, 4H), 2.05 (m, 1H), 1.9 (m, 1H), 1.5 (m, 1H), 1.5 (d, 2H), 1.4 (d, 1H).

20

EXAMPLE 27**2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-imidazo[4,5-c]pyridine**

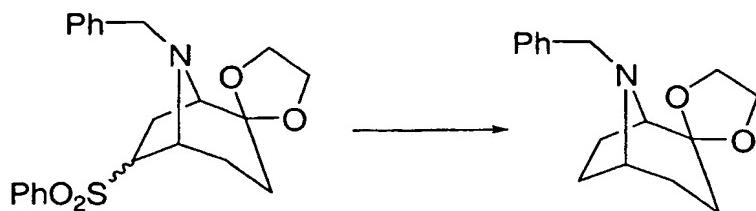
Example 27 was prepared in a similar manner to Example 25, but substituting 1-(2-trimethylsilyl-ethoxymethyl)-1H-imidazo[4,5-c]pyridine-2-carbaldehyde for 3-(2-trimethylsilyl-ethoxymethyl)-3H-imidazo[4,5-b]pyridine-2-carbaldehyde: MS ( $m+1$ ) = 335.5; <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) 9.02 (s, 1H), 8.4 (m, 1H), 7.5 (s, 1H), 7.3 - 7.1 (m, 5H), 3.9 (s, 2H), 3.22 (s, 2H), 2.78 (d, 0.65 x 2H), 2.55 (d, 0.35 x 2H), 2.18 (m, 4H), 2.05 (m, 1H), 1.9 (m, 1H), 1.65 (d, 1H), 1.5 (m, 2H), 1.4 (d, 1H).

EXAMPLE 28

(+)8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol and (-)-8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol

Example 28 was prepared by the following procedure.

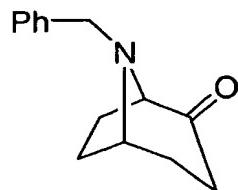
20 Step 1:



**(±)-8-Benzyl-8-aza-bicyclo[3.2.1]octan-2-one ethylene acetal:**

The procedure described in *Synth. Commun.*, 25:3681-3690 (1995) to prepare the analogous 8-methyl compounds was used. In a three-neck flask equipped with a thermometer, an argon inlet, and a powder funnel were placed sodium hydrogenphosphate (dibasic) (7.10g, 50.0mmol), and dry methanol (8mL). A solution of ( $\pm$ )-6-benzenesulfonyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one ethylene acetal (*J. Heterocyclic Chem.*, 34:1139-1146(1997) (2.00g, 5.0mmol) in tetrahydrofuran (16mL) was added. Sodium mercury amalgam (20% sodium) (5g) was added portionwise with stirring at such a rate as to keep the temperature below 50°C. The mixture was stirred an additional 1.5h at ambient temperature. The organic solution was decanted away from the inorganic residue. The inorganic residue was washed with tetrahydrofuran (3X8mL). The combined organic portion was concentrated under reduced pressure. The residue was dissolved in water (32mL) and extracted 10 with dichloromethane (4X16mL). The combined extract was washed with brine (20mL), dried (sodium sulfate), filtered, and the solvent was evaporated under reduced pressure to give crude product (1.21g, 89%) as an oil.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.44 (2H, d, *J* 7.5 Hz), 7.4 (3H, m), 3.9 (3H, m), 3.77 (1H, m), 3.65 (1H, d, *J* 14 Hz), 3.53 (1H, d, *J* 14 Hz), 3.19 (1H, m), 2.95 (1H, d, *J* 7 Hz), 2.03-1.85 (3H, m), 1.75 (1H, m), 1.65 (1H, m), 1.59 (2H, m), 1.41 (1H, m).

**Step 2:**



**(±)-8-Benzyl-8-aza-bicyclo[3.2.1]octan-2-one:**

The procedure described in *Synth. Commun.*, **25**:3681-3690 (1995) to prepare the analogous 8-methyl compounds was used. This intermediate product has been described in Blarney and Markwell, EP 76089 A2 830406. Further, the (+)- and (-)-enantiomers were described in *J. Org. Chem.*, **63**:4069-4078(1998).

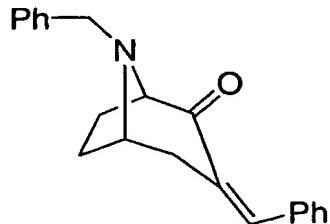
5       A solution of ( $\pm$ )-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one ethylene acetal (9.47g, 36.5mmol) in 3N perchloric acid (243mL, 20equiv.) was stirred at 90°C for 18h. The solution was cooled to ambient temperature and poured into ice-cold 3N sodium hydroxide solution (250mL). The mixture was extracted with dichloromethane (3X175mL). The combined extract was washed with brine (100mL), dried (sodium sulfate), filtered, and the solvent was evaporated under reduced pressure to give crude product (8.23g).

10      The crude product was dissolved in dichloromethane (200mL), di-*tert*-butyl dicarbonate (3.24mL, 15.0mmol) was added, and the solution was stirred at ambient temperature for 18h. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (20:80 increasing to 50:50).

15      The first compound to elute was ( $\pm$ )-benzyl-(7-oxo-cyclohept-3-enyl)-carbamic acid *tert*-butyl ester (1.00g, 9%), followed by product ( $\pm$ )-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one (2.88g, 37%) as a pale yellow oil, followed by mixed product/recovered ( $\pm$ )-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one ethylene acetal (3.31g). The mixed product/recovered starting material was recycled in 3N perchloric acid (30mL) to afford additional product (2.77g, 35%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.33 (4H, m), 7.25 (1H, m), 3.68 (2H, s), 3.36 (2H, d, *J* 6 Hz), 2.42-2.30 (2H, m), 2.20 (4H, m), 1.75 (2H, m).

25

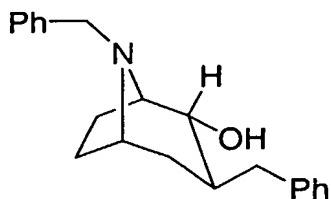
### Step 3:



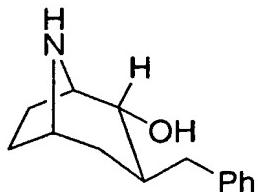
**( $\pm$ )-8-Benzyl-3-benzylidene-8-aza-bicyclo[3.2.1]octan-2-one:**

A 5N sodium hydroxide solution (1.62mL, 0.5equiv.) was added to ( $\pm$ )-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one (3.49g, 16.2mmol), followed by a solution of benzaldehyde (2.59mL, 2.69g, 16.2mmol) in ethanol (160mL). The solution was stirred at ambient temperature for 4.5h. The solution was concentrated under reduced pressure, and the residue was taken up in dichloromethane (160mL).  
 5 The mixture was washed with water (160mL) and brine (160mL), dried (sodium sulfate), filtered, and the solvent evaporated under reduced pressure to give crude product (4.96g, theoretical yield 4.92g) as an orange oil.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.64 (1H, s), 7.47 (2H, d, *J* 14 Hz), 7.41-7.24 (8H, m), 3.77 (2H, s), 3.66 (1H, d, *J* 7.5 Hz), 3.53 (1H, t, *J* 6 Hz), 3.18 (1H, m), 2.66 (1H, d, *J* 17 Hz),  
 10 2.31 (1H, m), 2.18 (1H, m), 1.79 (1H, m), 1.59 (1H, m).

**Step 4:**

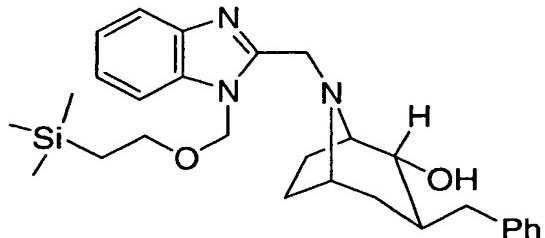


15 **( $\pm$ )-3-exo-Benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol:**  
 A mixture of crude ( $\pm$ )-8-benzyl-3-benzylidene-8-aza-bicyclo[3.2.1]octan-2-one (4.95g, 16.2mmol) and platinum(IV) oxide (0.30g) in methanol (80mL) was hydrogenated on a Parr hydrogenation apparatus (51psi) for 42h. The catalyst was removed by filtration through Celite®. The filter cake was washed with methanol (3X40mL) and the filtrate was concentrated under reduced pressure to give a yellow gum (4.98g). The gum was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (25:75 increasing to 67:33). The first compound to elute was the epimeric byproduct ( $\pm$ )-3-exo-benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-exo-ol (0.34g, 7%), as an oil, followed by the  
 20 partial reduction byproduct ( $\pm$ )-8-benzyl-3-benzylidene-8-aza-bicyclo[3.2.1]octan-2-endo-ol (1.14g, 23%), as an oil, followed by the product (1.98g, 40%), as a white solid, m.p. 104-105°C.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.37-7.25 (7H, m), 7.19 (3H, m), 3.57 (1H, m), 3.52 (2H, d, *J* 6 Hz), 3.09 (3H, m), 2.36 (1H, m), 1.98 (1H, m), 1.83 (2H, m), 1.58 (1H, m), 1.45 (4H, m).  
 25 30 Mass spec.: 308.4 (M+1).

**Step 5:****(±)-3-exo-Benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol:**

5 A mixture of ( $\pm$ )-3-exo-benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol (1.97g, 6.4mmol) and 10% palladium on carbon (0.60g) in methanol (80mL) was hydrogenated on a Parr hydrogenation apparatus (51psi) for 18h. The catalyst was removed by filtration through Celite®. The filter cake was washed with methanol (3X40mL) and the filtrate was concentrated under reduced pressure to give 10 crude product (1.39g). The crude product was dissolved in dichloromethane and filtered through a pad of silica gel eluting with methanol:dichloromethane:concentrated ammonium hydroxide (20:80:2). The filtrate was concentrated under reduced pressure to give product (1.36g, 98%) as a solid white foam.

15  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.28 (2H, m), 7.18(3H, m), 3.40 (3H, m), 3.09 (1H, dd,  $J$  13, 4 Hz), 2.37 (1H, m), 1.91 (2H, m), 1.88-1.61 (4H, m), 1.42 (2H, m), 1.30 (1H, m). Mass spec.: 218.2 (M+1).

**Step 6:**

20

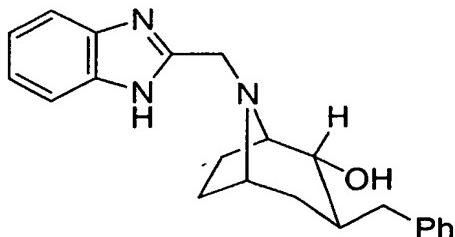
**(±)-3-exo Benzyl-8-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-endo-ol:**

To a mixture of ( $\pm$ )-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol (1.35g, 6.2mmol) in dichloromethane (6mL) under an atmosphere of argon was added

a solution of 1-(2-trimethylsilyl-ethoxymethyl)-1*H*-benzimidazol-2-carbaldehyde (2.05g, 7.4mmol) in dichloromethane (6mL). The mixture was stirred 15 minutes and sodium triacetoxyborohydride (1.57g, 7.4mmol) was added. The mixture was stirred 62h at ambient temperature. The mixture was diluted with ethyl acetate (75mL), 5 washed with saturated sodium bicarbonate solution (2X35mL), water (35mL), and brine (35mL). The organic solution was dried (sodium sulfate), filtered, and the solvent evaporated under reduced pressure to give crude product (3.07g) as an orange solid. The crude product was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (50:50) increasing to ethyl acetate (100%) to give 10 product (1.75g, 59%) as a pale yellow solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.76 (1H, dd, *J* 6.5, 2 Hz), 7.52 (1H, dd, *J* 6.5, 2 Hz), 7.30 (4H, m), 7.20 (3H, m), 5.85 (2H, dd, *J* 19, 11 Hz), 3.90 (2H, d, *J* 2 Hz), 3.59 (2H, t, *J*, 8 Hz), 3.53 (1H, m), 3.18 (2H, m), 3.10 (1H, dd, *J* 13, 4 Hz), 2.36 (1H, dd, *J* 13, 9 Hz), 2.10 (1H, m), 1.98 (1H, m), 1.91 (1H, m), 1.63 (2H, m), 1.51 (1H, d, *J* 5 Hz), 1.46 (1H, m), 15 1.38 (1H, m), 0.95 (2H, t, *J*, 8 Hz), 0.04 (9H, s).

### Step 7:



( $\pm$ )-8-(1*H*-Benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol:

To a suspension of ( $\pm$ )-3-*exo* Benzyl-8-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol (1.74g, 3.65mmol) in ethanol (24mL) was added 3N hydrochloric acid (3ml, 2.5equiv.). The mixture was stirred for 6h at 80°C. The cooled solution was 20 concentrated under reduced pressure. The residue was taken up in ethyl acetate (250mL), washed with saturated sodium bicarbonate solution (2X100mL), water (100mL), and brine (100mL). The organic solution was dried (sodium sulfate), filtered, and the solvent evaporated under reduced pressure to give crude product 25 (1.23g, 100%) as a yellow solid. A portion (60mg) of the crude product was

chromatographed on a silica gel prep plate (1mm), eluting with methanol:dichloromethane:concentrated ammonium hydroxide (10:90:1) to give a yellow solid (40mg). The solid was triturated with ethyl acetate, filtered off, and dried in vacuo to give product (32mg) as a white solid, m.p. 218-219°C.

5       $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 9.63 (1H, br, s), 7.70 (1H, dd,  $J$  6, 2 Hz), 7.50 (1H, dd,  $J$  6, 2 Hz), 7.31-7.18 (7H, m), 3.82 (2H, d,  $J$  1Hz ), 3.62 (1H, d,  $J$ , 10 Hz), 3.12 (3H, m), 2.42 (1H, dd,  $J$  13, 9 Hz), 2.01 (1H, m), 1.91 (2H, m), 1.65 (2H, m), 1.48 (1H, m), 1.41 (2H, m).

Analysis calculated for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}$  C, 76.05; H, 7.25; N, 12.09.

10     Found: C, 76.15; H, 6.98; N, 12.09.

(+)-8-(1*H*-Benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol and (-)-8-(1*H*-Benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol:

15     Crude ( $\pm$ )-8-(1*H*-benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol (1.23g) was resolved by preparative chiral HPLC (three runs, Chiralcel™ OD column, 5x50 cm, hexane:isopropanol:diethylamine 80:20:0.1, 60mL/min at 210nm).

The first enantiomer to elute was (-)-8-(1*H*-benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol (0.65g) as a solid white foam, RT = 18.9min. The dihydrochloride salt melted at 234-236°C.

Mass spec.:348.4 (M+1).

$[\alpha]_D$  -92.2° (c 0.500, methanol).

Analysis calculated for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O} \cdot 2 \text{ HCl}$  C, 62.86; H, 6.47; N, 10.00.

25     Found: C, 62.54; H, 6.29; N, 9.89.

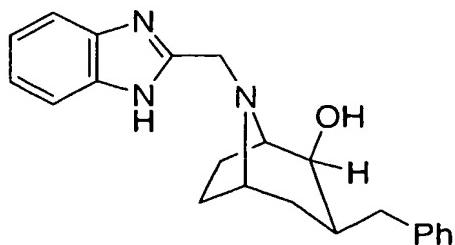
The second enantiomer to elute was (+)-8-(1*H*-benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol (0.58g) as a solid white foam, RT = 34.0min. The dihydrochloride salt melted at 234-236°C.

Mass spec.:348.4 (M+1).

30      $[\alpha]_D$  +95.0° (c 0.545, methanol).

Analysis calculated for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O} \cdot 2 \text{ HCl} \cdot 0.05 \text{ ethanol} \cdot 0.40 \text{ water}$  C, 61.74; H, 6.49; N, 9.78.

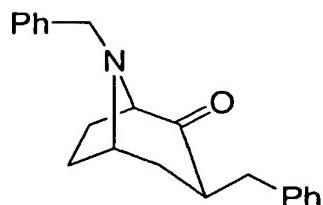
Found: C, 61.75; H, 6.23; N, 9.71.

EXAMPLE 29

(+)-8-(1*H*-Benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol and (-)-8-(1*H*-Benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol

5

Example 29 was prepared by the following procedure.

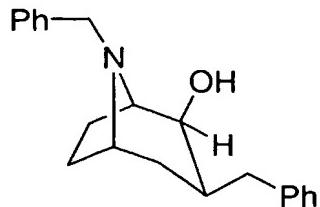
**Step 1:****(±)-3-exo-Benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one:**

10 A mixture of crude (±)-8-benzyl-3-benzylidene-8-aza-bicyclo[3.2.1]octan-2-one (7.08g, 22mmol) and 10% palladium on carbon (0.75g) in methanol (200mL) was hydrogenated (1atm) for 18 hours. The catalyst was removed by filtration through Celite. The filter cake was washed with methanol (3X75mL) and the filtrate was concentrated under reduced pressure to give crude product (6.10g, 15 91%), as a yellow oil.

An aliquot of product (100mg) was chromatographed on a 2mm silica prep plate eluting with ethyl acetate:hexane (20:80) to give purified product (61mg) as a pale amber oil.

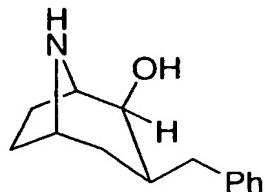
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.28 (7H, m), 7.18 (3H, m), 3.61 (2H, s), 3.42 (1H, d, *J* 7 Hz), 3.32 (2H, m), 2.61 (1H, m), 2.51 (1H, m), 2.17 (2H, m), 1.87-1.67 (4H, m).

20 Mass spec.: 306.4 (M+1).

**Step 2:****(±)-3-exo-Benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-exo-ol:**

To a solution of ( $\pm$ )-3-exo-benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-one (3.05g, 10.0mmol) in dry toluene (150mL) cooled to -50°C (dry ice/chloroform bath) was added dropwise over six minutes a solution of diisobutylaluminum hydride in toluene (1.5M, 23.3mL, 3.5equiv.). The solution was stirred one hour at -50°C. To the solution were added dropwise water (4mL), 3N sodium hydroxide solution (4mL), and water (12mL). The mixture was dried (magnesium sulfate), filtered, and the solvent evaporated under reduced pressure to give crude product (2.50g, 81%) as a yellow oil. The crude product was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (25:75) increasing to ethyl acetate (100%).

The first compound to elute was product (1.375g, 45%), as an oil, followed by the epimeric byproduct ( $\pm$ )-3-exo-benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol (0.38g, 12%), as a white solid.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.36 (4H, m), 7.27 (4H, m), 7.20 (2H, m), 3.45 (2H, dd, *J* 12, 21 Hz), 3.27 (1H, m), 3.21 (1H, d, *J* 5 Hz), 3.11 (1H, d, *J* 3 Hz), 2.75 (1H, dd, *J* 12, 8 Hz), 2.47 (1H, dd, *J* 13, 7 Hz), 1.97 (2H, m), 1.70 (1H, m), 1.52 (4H, m), 1.30 (1H, m).  
Mass spec.: 308.4 (M+1).

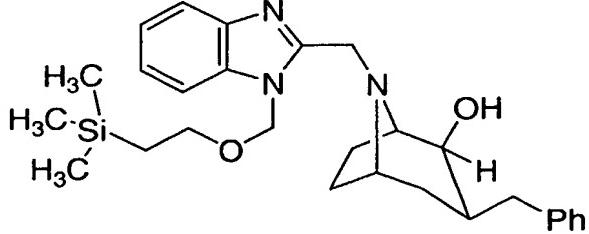
**Step 3:****(±)-3-exo-Benzyl-8-aza-bicyclo[3.2.1]octan-2-exo-ol:**

A mixture of ( $\pm$ )-3-*exo*-benzyl-8-benzyl-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol (2.80g, 9.1mmol) and 10% palladium on carbon (0.85g) in methanol (75mL) was hydrogenated on a Parr hydrogenation apparatus (52psi) for 18h. The catalyst was removed by filtration through Celite®. The filter cake was washed with 5 methanol (3X40mL) and the filtrate was concentrated under reduced pressure to give crude product (2.17g). The crude product was purified by flash column chromatography on silica gel, eluting first with ethyl acetate/hexane (50:50) to remove impurities, then eluting with methanol:dichloromethane:concentrated ammonium hydroxide (20:80:2) to give product (1.81g, 92%), as a pale yellow oil that crystallized 10 on standing, m.p. 92-94°C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.28 (2H, m), 7.20(3H, m), 3.42 (2H, m), 3.30 (1H, t, *J* 3 Hz), 2.74 (1H, dd, *J* 13, 8 Hz), 2.47 (1H, dd, *J* 13, 7 Hz), 2.2-1.8 (1H, br s), 1.75-1.61 (5H, m), 1.51 (2H, m), 1.30 (1H, m).

Mass spec.: 218.2 (M+1).

15

**Step 4:****( $\pm$ )-3-*exo* Benzyl-8-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol:**

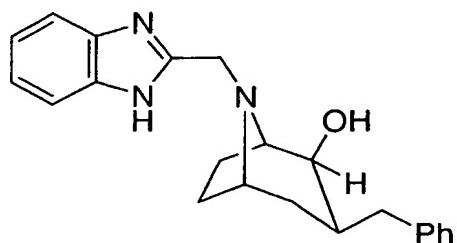
To a solution of ( $\pm$ )-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol (1.52g, 7.0mmol) in dichloromethane (4mL) under an atmosphere of argon was added 1-(trimethylsilyl)imidazole (1.10mL, 1.05g, 7.5mmol). The solution was stirred two hours at ambient temperature. The solvent was evaporated under reduced pressure to give crude ( $\pm$ )-3-*exo*-benzyl-2-(*exo*-trimethyl-silanyloxy) 8-aza-bicyclo[3.2.1]octane (2.60g) as an orange oil. Employing the procedure substantially as described above for ( $\pm$ )-3-*exo* benzyl-8-[1-(2-trimethylsilyl-ethoxymethyl)-1*H*-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol, but substituting crude ( $\pm$ )-3-*exo*-benzyl-2-(*exo*-trimethyl-silanyloxy) 8-aza-bicyclo[3.2.1]octane (2.60g, 7mmol) for 20

25

( $\pm$ )-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol, the product (2.36g, 71%) was obtained as an orange gum.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.76 (1H, dd, *J* 7, 2 Hz), 7.50 (1H, dd, *J* 7, 2 Hz), 7.29 (4H, m), 7.21 (3H, m), 5.72 (2H, s), 3.83 (2H, dd, *J* 14, 13 Hz), 3.73 (2H, t, *J*, 8 Hz), 3.60 (1H, m), 3.31 (3H, m), 2.77 (1H, dd, *J* 13, 8 Hz), 2.48 (1H, dd, *J* 13, 7 Hz), 2.11 (2H, m), 1.74 (1H, m), 1.66-1.45 (2H, m), 1.32 (2H, m), 1.08 (2H, t, *J*, 8 Hz), 0.05 (9H, s).

**Step 5:**



10 ( $\pm$ )-8-(1*H*-Benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol:

Employing the procedure substantially as described above for ( $\pm$ )-8-(1*H*-benzimidazol-2-ylmethyl)-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol, but substituting ( $\pm$ )-3-*exo* benzyl-8-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-*exo*-ol (2.34g, 4.9mmol) for ( $\pm$ )-3-*exo* benzyl-8-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol, the product (1.34g, 79%) was obtained as a solid yellow foam. A portion (149mg) of the crude product was chromatographed on a silica gel prep plate (1mm), eluting with

20 methanol:dichloromethane:concentrated ammonium hydroxide (10:90:1) to give a yellow solid (107mg). The solid was triturated with ethyl acetate, filtered off, and dried in vacuo to give product (79mg) as a white solid, m.p. 208-209°C.

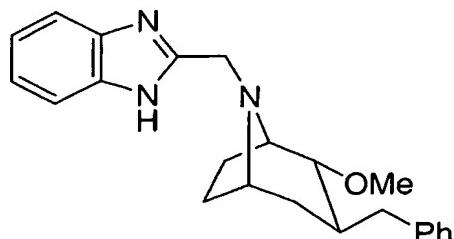
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 10.16 (1H, br, s), 7.71 (1H, br s), 7.42 (1H, br s), 7.25 (4H, m), 7.18 (3H, m), 3.81 (2H, dd, *J* 30, 15Hz), 3.43 (1H, s), 3.32 (1H, m), 3.20 (1H, d, *J* 3 Hz), 2.77 (1H, dd, *J* 13, 8 Hz), 2.51 (1H, dd, *J* 13, 7 Hz), 2.03 (2H, m), 1.81 (1H, m), 1.72-1.49 (4H, m), 1.40 (1H, m).

Mass spec.: 348.4 (M+1).

Analysis calculated for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O (•0.05 ethyl acetate •0.25 water) C, 74.82; H, 7.26; N, 11.70.

Found: C, 74.73; H, 6.99; N, 11.89.

EXAMPLE 30

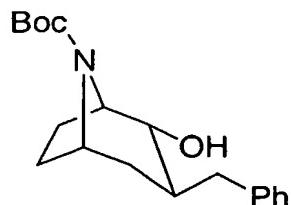


5

**(±)-2-(3-exo-Benzyl-2-endo-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole**

Example 30 was prepared by the following procedure.

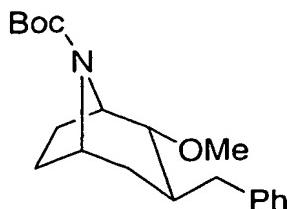
**Step 1:**



10

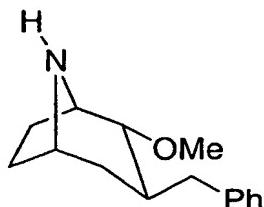
**(±)-3-exo-Benzyl-2-endo-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester:**

- To a solution of (±)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol (240mg, 1.1mmol) in dichloromethane (5mL) under an atmosphere of argon was added di-*tert*-butyl dicarbonate 0.276mL, 262mg, 1.2mmol). The solution was stirred 15 hours at ambient temperature. The solution was diluted with dichloromethane (10mL), washed with water (5mL), and brine (5mL), dried (sodium sulfate), filtered, and the solvent evaporated under reduced pressure to give crude product (384mg, theoretical yield 349mg) as a colorless oil.
- 20 Mass spec.: 318, 218.2 (M+1).

**Step 2:**

**( $\pm$ )-3-exo-Benzyl-2-endo-methoxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid  
tert-butyl ester:**

5           Potassium hydride (25% in mineral oil) was placed in a round-bottom flask under a stream of argon and washed with hexane to remove mineral oil. The washed potassium hydride was suspended in dry tetrahydrofuran (2mL). The mixture was cooled in an ice-bath and methyl iodide (0.081mL, 185mg, 1.3mmol) was added. A solution of crude ( $\pm$ )-3-exo-benzyl-2-endo-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (382mg, 1.1mmol) in dry tetrahydrofuran (2mL) was added dropwise over five minutes. The mixture was stirred with cooling for 15 minutes, then at ambient temperature for one hour. Saturated sodium bicarbonate solution (3mL) was added dropwise, and the mixture was extracted with ethyl acetate (3X15mL). The combined extract was washed with water (5mL) and brine (5mL), dried (sodium sulfate), filtered, and the solvent was evaporated under reduced pressure to give crude product (350mg, 96%) as an oil. The crude product was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (25:75) to give product (247mg, 68%) as a pale yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.26 (2H, m), 7.14(3H, m), 4.55-4.05 (3H, m), 3.44 (3H, s), 3.15-2.94 (2H, m), 2.29 (1H, m), 1.99-1.76 (4H, m), 1.58-1.24 (11H, m).

**Step 3:**

**( $\pm$ )-3-exo-Benzyl-2-endo-methoxy-8-aza-bicyclo[3.2.1]octane:**

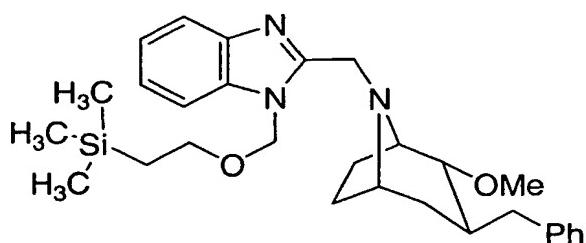
A mixture of ( $\pm$ )-3-*exo*-benzyl-2-*endo*-methoxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (245mg, 0.74mmol), dioxane (1.5mL), and 3N hydrochloric acid (1.0mL, 4equiv.) was heated at reflux for 3.5h. The cooled mixture was made basic with saturated sodium carbonate solution and extracted with dichloromethane (3X10mL). The combined extract was washed with brine (5mL), dried (sodium sulfate), filtered, and the solvent was evaporated under reduced pressure to give crude product (155mg, 91%) as a yellow oil.

5 Mass spec.:232.3 (M+1).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 3.42 (3H, s, -OCH<sub>3</sub>).

10

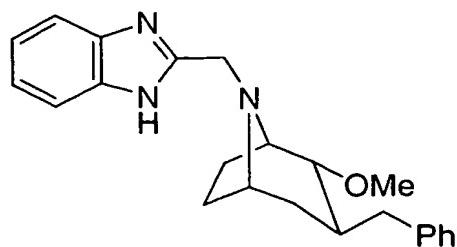
**Step 4:**



**( $\pm$ )-2-(3-*exo*-Benzyl-2-*endo*-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole:**

15 Employing the procedure substantially as described above for ( $\pm$ )-3-*exo* benzyl-8-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol, but substituting ( $\pm$ )-3-*exo*-benzyl-2-*endo*-methoxy-8-aza-bicyclo[3.2.1]octane for ( $\pm$ )-3-*exo*-benzyl-8-aza-bicyclo[3.2.1]octan-2-*endo*-ol:  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.76 (1H, dd, J 7, 1 Hz), 7.52 (1H, dd, J 7, 2 Hz), 7.28 (4H, m),  
20 7.18 (3H, m), 5.86 (2H, dd, J 31, 11 Hz), 3.90 (2H, s), 3.60 (2H, t, J, 8 Hz), 3.45 (1H, m), 3.36 (3H, d, J 1 Hz), 3.15 (2H, m), 2.99 (1H, dd, J 10, 3.5 Hz), 2.23 (1H, dd, J 13, 10 Hz), 2.08 (1H, m), 1.92 (2H, m), 1.62 (1H, m), 1.43 (1H, m), 1.29 (2H, m), 0.95 (2H, t, J, 8 Hz), 0.03 (9H, s).

25 **Step 5:**



**(±)-2-(3-exo-Benzyl-2-endo-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole:**

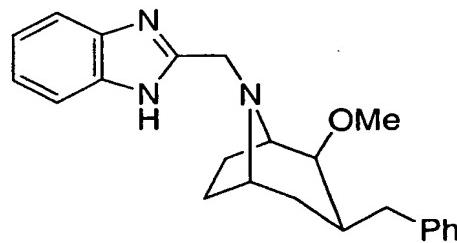
- Following the procedure substantially as described in Step 7, Example 28 above, the product precipitated from the reaction mixture as the dihydrochloride salt, m.p. 222-226°C.
- 5       $^1\text{H}$  NMR (DMSO-d<sub>6</sub>) 7.70 (2H, dd, *J* 6, 3 Hz), 7.34 (2H, dd, *J* 6, 3 Hz), 7.28 (2H, m), 7.18 (3H, m), 4.48 (2H, m), 4.36 (1H, br s), 4.00 (1H, br s), 3.50 (1H, d, *J* 10 Hz), 3.36 (3H, s), 3.03 (1H, dd, *J* 13, 3 Hz), 2.34 (1H, m), 2.27 (1H, m), 2.08 (3H, m), 1.84 (1H, m), 1.72 (2H, m), 1.43 (1H, d, *J* 13.5 Hz).
- 10     Mass spec.: 362.4 (M+1).

Analysis calculated for C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O•2 HCl C, 63.59; H, 6.73; N, 9.67.

Found: C, 63.57; H, 6.53; N, 9.74.

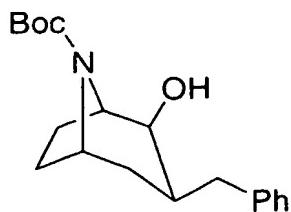
15

**EXAMPLE 31**



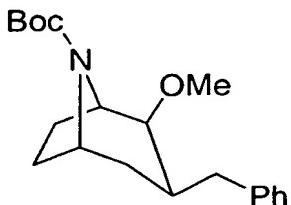
**(±)-2-(3-exo-Benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole**

Example 31 was prepared by the following procedure.

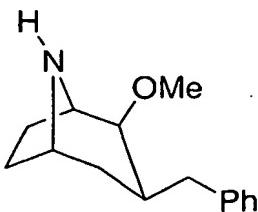
**Step 1:****(±)-3-exo-Benzyl-2-exo-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid  
tert-butyl ester:**

5 Employing the procedure substantially as described above for Example 30, but substituting (±)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-exo-ol (240mg, 1.1mmol) for (±)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol, the product (389mg, theoretical yield 349mg) was obtained as a colorless oil.  
Mass spec.: 318.2, 218.2 (M+1).

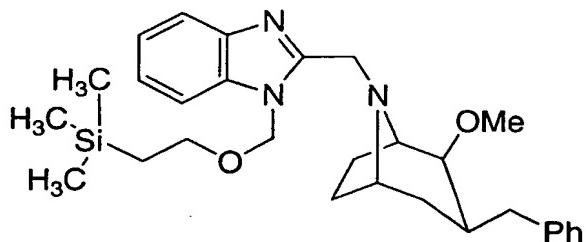
10

**Step 2:****(±)-3-exo-Benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid  
tert-butyl ester:**

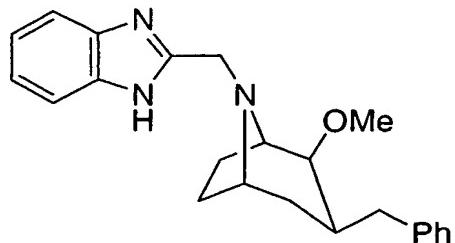
15 Employing the procedure substantially as described above, but substituting (±)-3-exo-benzyl-2-exo-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (387mg, 1.1mmol) for (±)-3-exo-benzyl-2-endo-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester, the product (272mg, 75%) was obtained as a pale yellow oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.26 (2H, m), 7.17(3H, m), 4.62-4.10 (3H, m), 3.36 (3H, d,  $J$  16 Hz), 2.81-2.65 (2H, m).

**Step 3:****(±)-3-exo-Benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]octane:**

- Employing the procedure substantially as described above, but
- 5 substituting ( $\pm$ )-3-exo-benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (265mg, 0.80mmol) for ( $\pm$ )-3-exo-benzyl-2-endo-methoxy-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester, the product (180mg, 97%) was obtained as a yellow oil.
- Mass spec.: 232.3 (M+1).
- 10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 3.32 (3H, s, - $\text{OCH}_3$ ).

**Step 5:****(±)-2-(3-exo-Benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazol-2-ylmethoxyethylsilane:**

- Employing the procedure substantially as described for ( $\pm$ )-3-exo-benzyl-8-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-ylmethyl]-8-aza-bicyclo[3.2.1]octan-2-endo-ol, but substituting ( $\pm$ )-3-exo-benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]octane for ( $\pm$ )-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-ol:
- 20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.76 (1H, d,  $J$  8 Hz), 7.53 (1H, d,  $J$  8 Hz), 7.29 (4H, m), 7.18 (3H, m), 6.15 (1H, d,  $J$ , 11 Hz), 6.01 (1H, d,  $J$ , 11 Hz), 3.90 (2H, dd,  $J$  24, 13 Hz), 3.62 (2H, t,  $J$ , 8 Hz), 3.50 (1H, m), 3.26 (1H, s), 3.09 (3H, s), 2.77 (1H, m), 2.73 (1H, m), 2.48 (1H, dd,  $J$  13, 6.5 Hz), 2.10 (2H, m), 1.89 (1H, m), 1.62 (2H, m), 1.37 (2H, m), 0.95 (2H, t,  $J$ , 8 Hz), 0.04 (9H, s).

**Step 6:**

5      **( $\pm$ )-2-(3-exo-Benzyl-2-exo-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-  
benzimidazole:**

The procedure followed was substantially as described in Step 7,  
Example 28: m.p. 172-173°C.  
10       $^1\text{H}$  NMR (DMSO-d<sub>6</sub>) 10.76 (1H, br s), 7.69 (1H, br s), 7.44 (1H, br s), 7.27 (3H, m),  
7.19 (4H, m), 3.82 (2H, s), 3.30 (2H, m), 3.29 (3H, d, *J* 1 Hz), 2.84 (1H, m), 2.78  
10 (1H, dd, *J* 13, 8 Hz), 2.60 (1H, dd, *J* 13, 7 Hz), 2.00 (3H, m), 1.79 (1H, m), 1.66 (1H,  
m), 1.42 (2H, m).

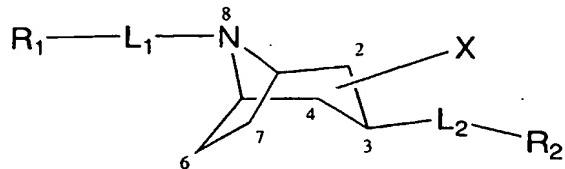
Mass spec.: 362.4 (M+1).

Analysis calculated for C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O: C, 76.42; H, 7.53; N, 11.94.

Found: C, 77.17; H, 7.43; N, 11.94.

## WHAT IS CLAIMED IS:

## 1. A compound having the formula:



- 5 or a pharmaceutically acceptable salt thereof, wherein  
 R<sub>1</sub> is benzimidazole, imidazole, imidazopyridine, indole, quinazoline,  
 purine, benzoxazolone, or phenol;
- R<sub>2</sub> is phenyl, optionally substituted with one to five substituents, each  
 substituent independently being chloro, fluoro, bromo, C<sub>1</sub>-C<sub>4</sub>alkyl, trifluoromethyl,  
 10 hydroxy, or carboxy;
- L<sub>1</sub> and L<sub>2</sub> are independently C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkenyl, C<sub>1</sub>-  
 C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, aminoC<sub>1</sub>-C<sub>4</sub>alkyl, hydroxyC<sub>1</sub>-C<sub>4</sub>alkyl, carbonyl, cycloC<sub>3</sub>-  
 C<sub>6</sub>alkyl or aminocarbonyl; and
- optionally substituted at any of the 2, 3, 4, 6, or 7 positions  
 15 independently with X, wherein X is hydroxy, amino, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-  
 C<sub>4</sub>)alkylamino, C<sub>1</sub>-C<sub>4</sub>alkyl, ester, carbamate, carbonate, or ether.

2. The compound according to claim 1, wherein R<sub>1</sub> is benzimidazole.

20 3. The compound according to claim 1, wherein R<sub>1</sub> is imidazole.

4. The compound according to claim 1, wherein R<sub>1</sub> is imidazopyridine.

5. The compound according to claim 1, wherein R<sub>1</sub> is purine.

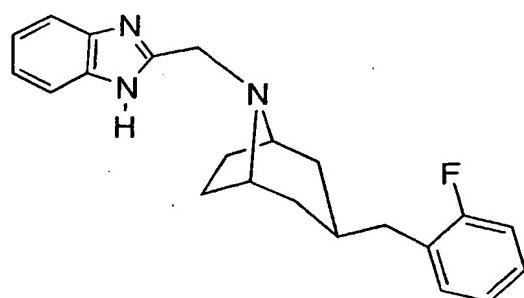
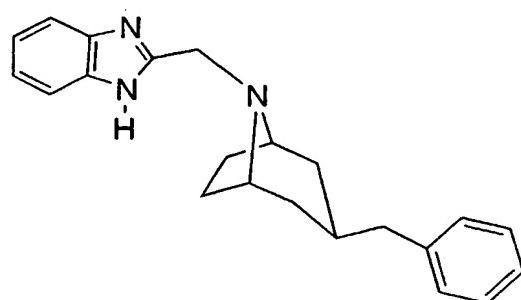
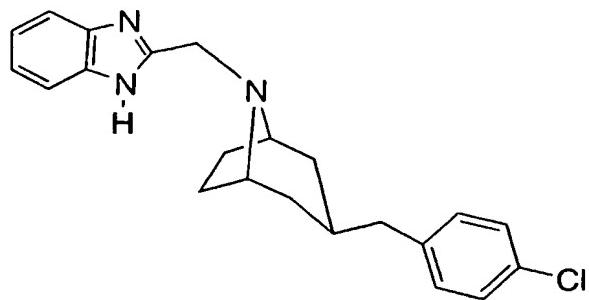
25 6. The compound according to claim 1, wherein R<sub>1</sub> is phenol.

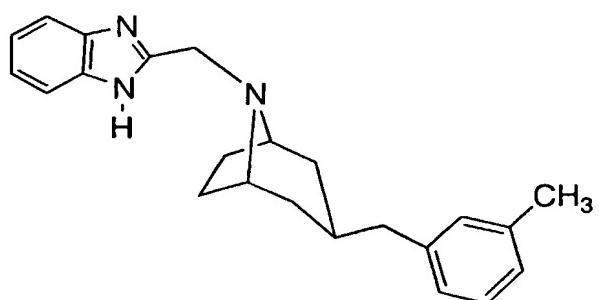
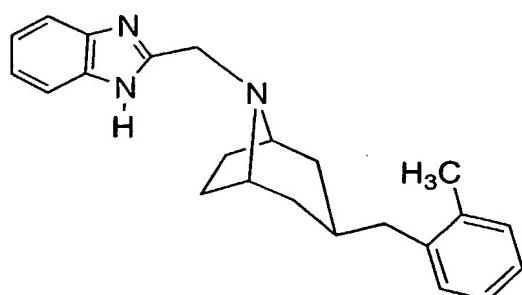
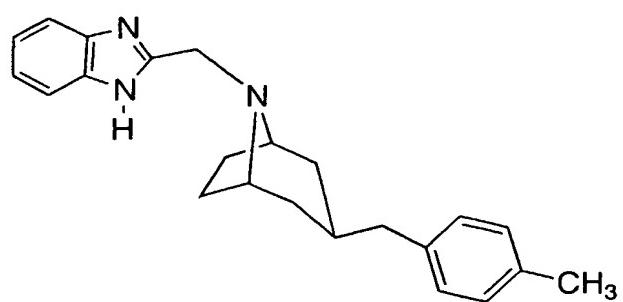
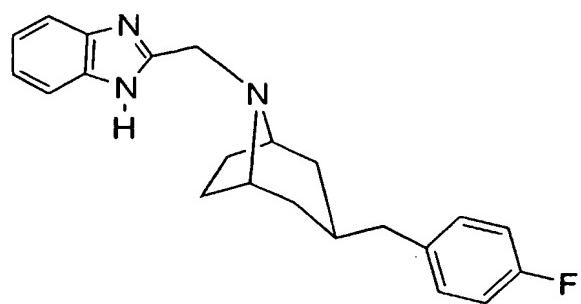
7. The compound according to claim 1, wherein said compound is  
 2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
 30 2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole;

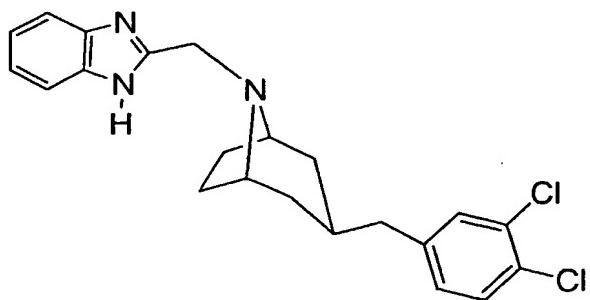
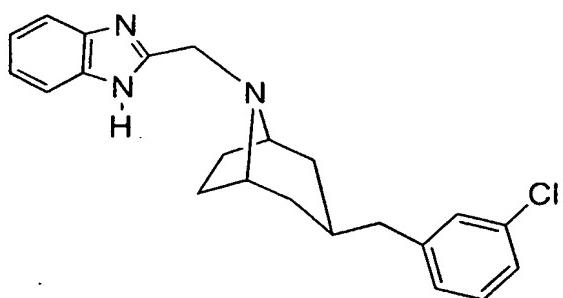
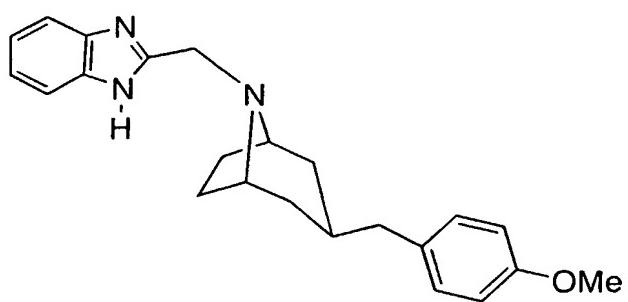
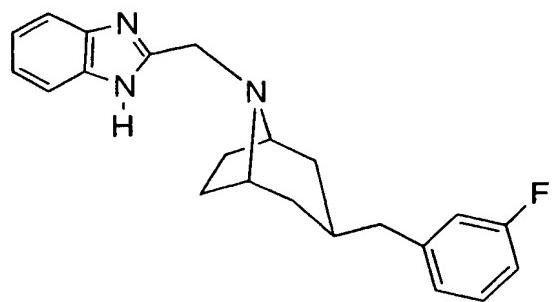
- 2-[3-(2-Fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(4-Fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(4-Methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(2-Methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;
- 5 2-[3-(3-Methyl-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(3-Fluoro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(4-Methoxy-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(3-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;  
2-[3-(3,4-Dichloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-1H-benzimidazole;
- 10 8-(1H-Benzimidazol-2-ylmethyl)-3-benzyl-8-aza-bicyclo[3.2.1]octan-6-ol;  
3-Benzyl-8-[3-(1H-imidazol-4-yl)-propyl]-8-aza-bicyclo[3.2.1]octane;  
4-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-phenol;  
4-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-ethyl]-phenol;  
4-{2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-phenol;
- 15 4-{3-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-propyl}-phenol;  
4-[2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-ethoxy]-phenol;  
4-{2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethoxy}-phenol;  
4-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-butyl]-phenol;  
8-(1H-Benzimidazol-2-ylmethyl)-8-aza-bicyclo[3.2.1]octane-3 -carboxylic acid 2-
- 20 fluoro-benzylamide;  
2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-1H-benzimidazole;  
2-[3-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-yl)-propyl]-3H-imidazo[4,5-b]pyridine;  
2-[3-(4-Chloro-benzyl)-8-aza-bicyclo[3.2.1]oct-8-ylmethyl]-3H-imidazo[4,5-  
b]pyridine;
- 25 2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-3H-imidazo[4,5-b]pyridine;  
8-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-9H-purine;  
2-(3-Benzyl-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-imidazo[4,5-c]pyridine;  
(+)-8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-  
ol;
- 30 (-)-8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-endo-  
ol;  
(+)-8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-exo-ol;  
(-)-8-(1H-Benzimidazol-2-ylmethyl)-3-exo-benzyl-8-aza-bicyclo[3.2.1]octan-2-exo-ol;  
(±)-2-(3-exo-Benzyl-2-endo-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-
- 35 benzimidazole; or

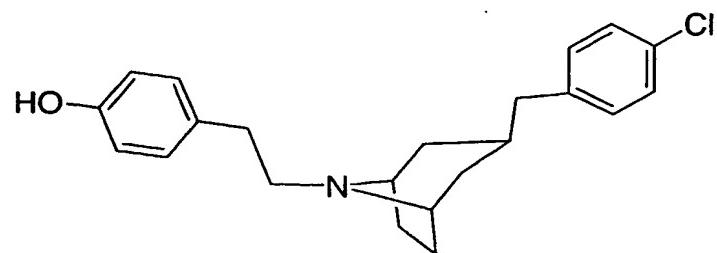
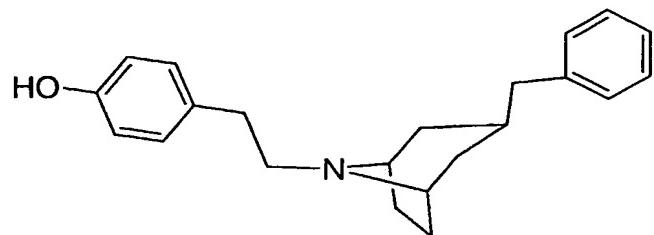
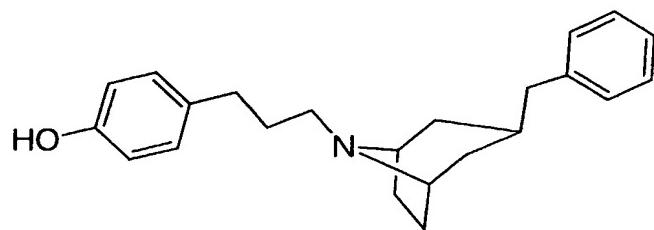
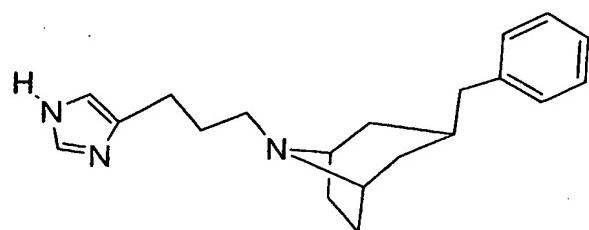
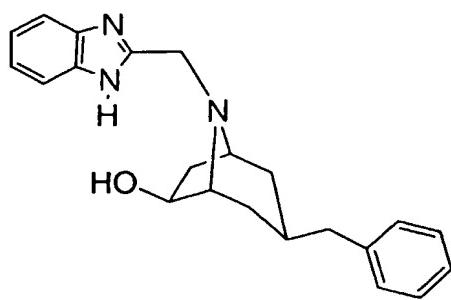
( $\pm$ )-2-(3-*exo*-Benzyl-2-*exo*-methoxy-8-aza-bicyclo[3.2.1]oct-8-ylmethyl)-1H-benzimidazole.

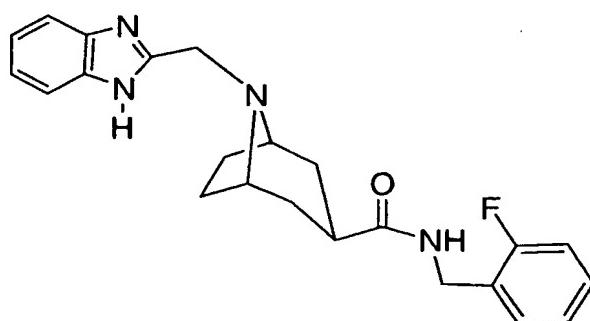
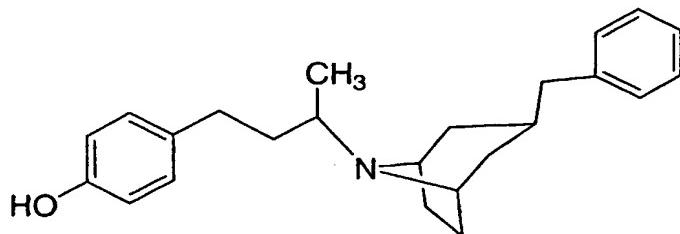
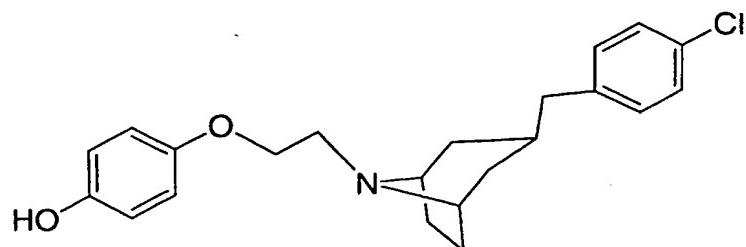
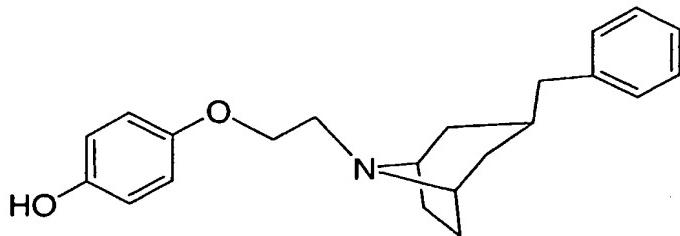
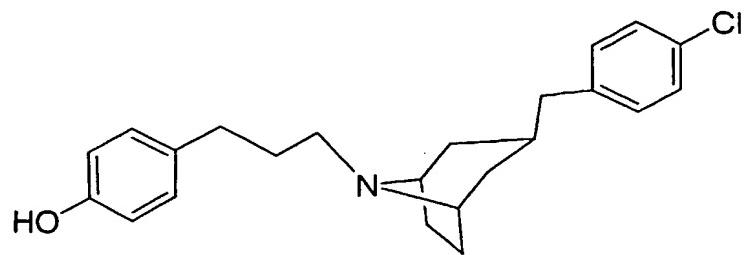
8. The compound according to claim 1, wherein said compound is

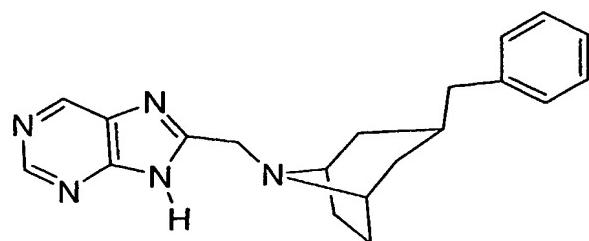
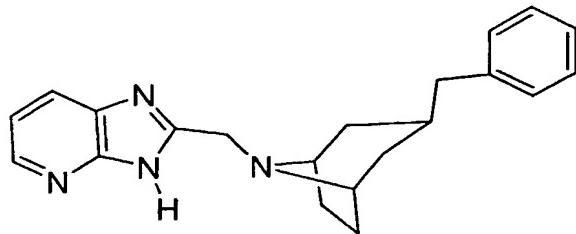
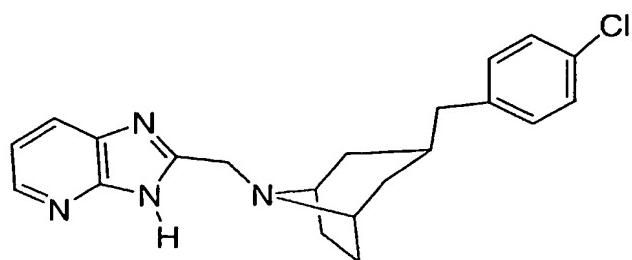
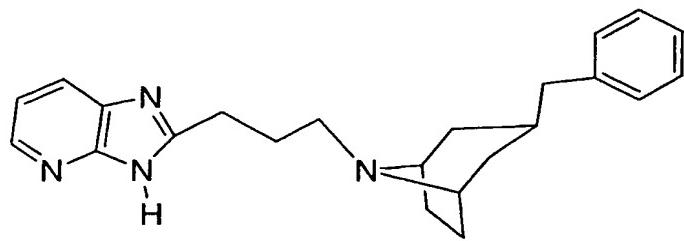
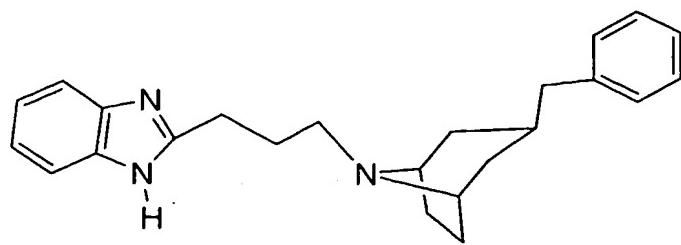


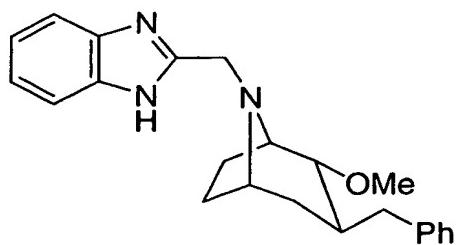
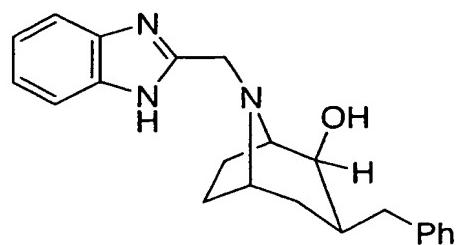
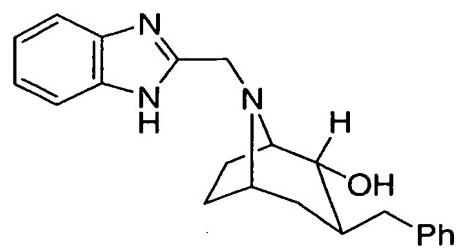
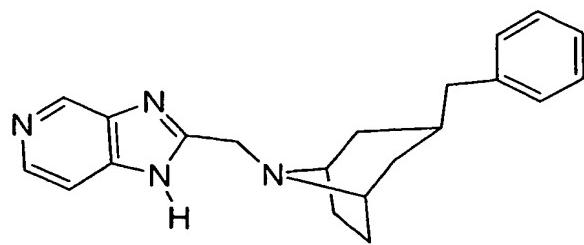




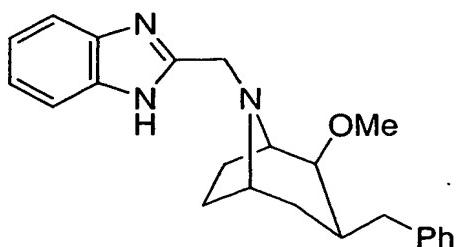








5 or



9. A pharmaceutical composition comprising an inert carrier and an effective amount of a compound according to claim 1.

5           10. The pharmaceutical composition according to claim 9 useful for the treatment of pain.

10          11. The pharmaceutical composition according to claim 9 useful for the treatment of migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke.

12. A method of treating migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 1.

15          13. A method of treating pain comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 1.

20

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/29479

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/46; A61P 29/02; C07D 401/06

US CL :514/304; 546/126

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/304; 546/126

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A         | US 5,714,498 A (KULAGOWSKI et al), see entire document.<br><i>03 February 2001</i> | 1-13                  |

 Further documents are listed in the continuation of Box C.  See patent family annex.

|   |     |  |
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| * Special categories of cited documents:  | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
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Date of the actual completion of the international search

09 JANUARY 2001

Date of mailing of the international search report

26 FEB 2001

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